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MALLORY-WEISS SYNDROME

A CASE WITH RECOVERY AFTER TOTAL GASTRECTOMY

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IN 1929 Mallory and Weiss recorded the case histories and post-mortem findings in 3 patients who died as a result of massive gastro-intestinal hæmorrhage following severe and continued vomiting. The macroscopical findings were strikingly constant and showed, at the site of hæmorrhage, 'fissure ulcers' 3–20 mm. in length and 2–3 mm. in breadth situated around the circumference of the cardiac opening with their long axis in line with the œsophagus. In two of these cases the lesions were limited to the stomach, extending almost to the border of the œsophagus, and in the third case the upper quarter of the ulcer extended into the œsophagus.

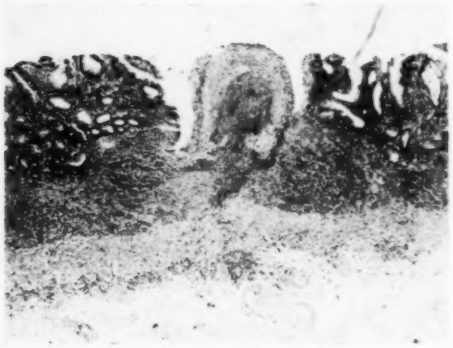


FIG. 1.—Section of 'fissure ulcer' showing hæmorrhagic necrosis of mucous membrane with adjacent changes of severe chronic gastritis. (× 24.)

On section there was ulceration of the mucosa extending to the muscularis and the floor of the ulcer was composed of fresh fibrin and an exudate of polymorphonuclear leucocytes. In one of the sections a ruptured arteriole was found. Chronic fibrous-tissue reaction was not observed.

The authors also found similar lesions, though no evidence of bleeding, at the post-mortem of a patient who died with prolonged vomiting due to toxic hepatitis. They further demonstrated that artificial distension of the stomach taken from a recently deceased person produced similar tears in the cardiac region if the œsophagus was occluded at the level of the diaphragm. They concluded that the lesions are caused by "pressure changes in the stomach during a disturbed mechanism of vomiting and continuous regurgitation of gastric juice over the cardia".

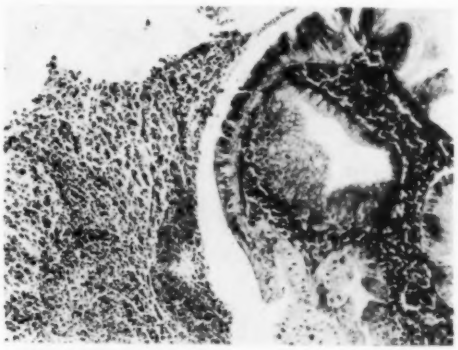


FIG. 2.—Section from edge of tissue ulcer showing necrotic material infiltrated with polymorphs and fibrin. The wall of the ulcer is lined by cells of a deep gland. (× 84.)

The following case is of interest as the typical lesions were found in a patient who had no previous history of vomiting and who recovered after a total gastrectomy had been performed for continuous bleeding.

CASE REPORT

Mrs. C. B., aged 53, was admitted to St. Thomas's Hospital on the evening of Dec. 30, 1954. She stated that after being perfectly well that morning she began to feel sick and vomited bright-red clots of blood for about half an hour and then fainted. In 1950 she had had a similar attack for which she had been treated at home and had not been further investigated. After admission to hospital she remained free from vomiting for six days, after which she had a severe hæmatemesis requiring a transfusion of 4 pints of blood to restore her circulatory condition.

On the following day she had an additional bleed and was given 8 pints of blood. Although no diagnosis was made her bleeding continued and operative interference was considered advisable.

AT OPERATION.—As no macroscopical intra-abdominal lesion was apparent the stomach was opened. Multiple small areas of gastric ulceration were seen, linear in shape and confined to the lesser curvature, being more numerous towards the cardiac end of the stomach and extending only half-way to the pylorus; they had a pustular appearance, with a congested periphery and a yellowish floor. A high Billroth I gastrectomy was performed. On the following day a further severe hæmatemesis occurred. As she was known to have further ulceration in the region of the cardia an unsuccessful attempt was made to control the hæmorrhage by the insertion of a Miller-Abbott balloon and applying traction. A further 8 pints of blood brought the systolic pressure to 80 mm. Hg, and as bright-red blood was running continuously from her mouth, it appeared that her only hope of survival lay in resecting the remainder of the stomach and œsophagogastric junction. This was carried out and continuity restored by means of an œsophagojejunal anastomosis. At the cardiac end of the stomach were situated five fissure-shaped ulcers, one of which encroached upon the œsophagus. They were 7–10 mm. in length and 1 mm. in breadth, with a yellow base and slightly reddened and raised edges. Further smaller but similar ulcerated areas extended half-way down the lesser curvature. Her post-operative course was stormy, but she survived and has maintained a steady weight over the last two years.

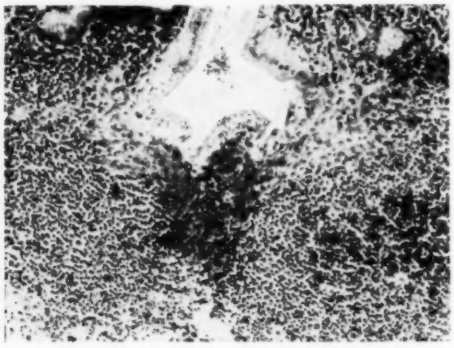


FIG. 3.—Section from the base of a deep gland showing early extravasation of blood from vascular plexus above the muscularis mucosæ. (× 84.)

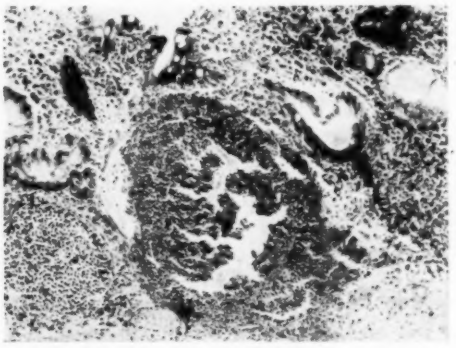


FIG. 4.—Section from base of mucosa showing hæmorrhagic extravasation leading to necrosis of tissue. (× 84.)

FIG. 5.—Section from œsophagogastric junction showing 'fissure ulcer' with portions of squamous epithelium and atrophic gastric mucosa. (× 24.)

HISTOLOGY.—

First Specimen.—Sections of stomach wall from the body and antrum show the appearances of severe chronic atrophic gastritis (*Fig.* 1). There is a uniform mucosal atrophy with irregularity of the surface epithelium, loss of acini and specialized secreting cells, and distortion of the remaining glands. The substantia propria is heavily infiltrated with chronic inflammatory cells, predominantly plasma cells with scattered eosinophils, and there is marked lymphoid hyperplasia. The inflammatory process extends through the muscularis mucosæ into the muscularis.

In the sections taken from the cardiac end of the stomach there are numerous small ulcers extending through the muscularis mucosa. The developed lesion is characterized by necrosis of the mucous membrane, the ulcer crater being full of red cells, fibrin, and polymorphs (*Fig.* 1). The edges of the ulcer are vertical and in some instances are lined at the side by the intact epithelium of a deep gland (*Fig.* 2). In the older lesions there is subacute inflammation of the underlying submucosa with focal collections of eosinophils and new capillary formation. A study of the mucous membrane between the ulcers suggests that the initial lesion is an extravasation of blood from the vascular plexus between the mucosa and the muscularis mucosa. This frequently starts at the base of a gland (*Fig.* 3), and then extends, leading to pressure necrosis over overlying mucosa and underlying muscularis mucosa (*Fig.* 4). The ulcer thus formed is secondarily infiltrated by fibrin and polymorphs.

No specific arteriolar lesions were seen.

Second Specimen.—Sections from the œsophagogastric junction show a fissure ulcer similar to that already described but involving the squamocolumnar junction (*Fig.* 5). Sections from the rest of the stomach show the appearances of severe chronic gastritis with, in addition, degenerative and necrotic changes consequent upon the trauma and ischæmia following the first operation.

DISCUSSION

Following the first report of 3 cases by Mallory and Weiss no further reports of this condition occurred until 1953 when Decker, Zamcheck, and Mallory reported 11 cases showing fissure ulceration

of the upper end of the stomach and/or cardiogastric junction. Their cases were all characterized by severe hæmatemesis, and as in the original description the lesions were thought to be lacerations consequent upon vomiting.

Of their 11 cases 5 were unassociated with other obvious disease, 4 were associated with reflex vomiting from disease elsewhere, and 2 with alcoholism. Eight of the cases showed definite histological evidence of chronic gastritis, and it was suggested that this may predispose to fissuring if vomiting occurs.

Although Decker and others suggested that vomiting is the principal aetiological factor, its duration in their series varied from 21 days to 12 hours, and in our case vomiting did not occur before the hæmatemesis. Consideration of the pathological findings in our case suggests that severe chronic atrophic gastritis was the primary lesion. It is known that this disease may give rise to occult bleeding and is a common cause of iron-deficiency anæmia, and the lesion occasionally gives rise to overt melæna or hæmatemesis (Joske, Finckh, and Wood, 1955).

In the present case the hæmorrhage appears to have occurred as a result of multiple lesions starting in the vascular plexus at the base of the mucosa leading to extravasation of red blood-cells with destruction of adjacent mucosa and muscularis mucosa.

These findings are similar to those described by Ivy, Grossman, and Bachrach (1950), who distinguish acute gastric erosions and ulcers due to primary interstitial hæmorrhage from the type in which there is a primary necrosis with subsequent hæmorrhage.

The essential difference between the lesions of the Mallory-Weiss syndrome and other cases of multiple acute erosions or ulcers is the linear nature of the lesions and their anatomical relationship to the folds of the mucosa in the region of the gastro-œsophageal junction. In the present case there is no evidence that vomiting precipitated the lesions, and it seems likely that when vomiting occurs it is related to some underlying disturbance.

The association of the fissure type ulcer with severe chronic gastritis is clearly shown and suggests that this may predispose to this particular type of lesion. No further evidence is available in the present case to indicate what precipitated the vascular abnormality which led to bleeding.

We are indebted to Dr. R. Hilton for permission to publish this case; Mr. W. C. Tanner for his assistance and advice in the management of the patient, and Mr. A. E. Clarke for the photographs.

REFERENCES

DECKER, J. P., ZAMCHECK, N., and MALLORY, G. K. (1953), *New Engl. J. med. Sci.*, **249**, 957.
IVY, A. C., GROSSMAN, M. I., and BACHRACH, W. H. (1950), *Peptic Ulcer*. London: Blakiston.
JOSKE, R. A., FINCKH, E. S., and WOOD, I. J. (1955), *Quart. J. Med.*, **48**, N.S. **24**, 269.
MALLORY, G. K., and WEISS, S. (1929), *Amer. J. med. Sci.*, **178**, 506.

IDIOPATHIC RETROPERITONEAL FIBROSIS

A CONDITION INVOLVING THE URETERS, THE AORTA, AND THE INFERIOR VENA CAVA

BY EARLE HACKETT

FROM THE SCHOOL OF PATHOLOGY, TRINITY COLLEGE, DUBLIN

IN 1948 J. K. Ormond described 2 cases of bilateral ureteral obstruction where the ureters were enveloped and compressed by an unusual retroperitoneal fibrotic lesion which had the nature of a scar, but for which there was no history or evidence of anything likely to excite scar tissue in such a site.

Since then, 18 further cases have been reported (Amselem, 1950; Oppenheimer, Narins, and Simon, 1952; Miller, Lipin, Meisel, and Long, 1952; Ewell and Bruskewitz, 1952; Bradfield, 1953; Chisholm, Hutch, and Bolomey, 1954; MacLean, 1954; Raper, 1955; Mirabile and Spillane, 1955; Raper, 1956; Case Records of the Massachusetts General Hospital, 1956, 1957) where a similar retroperitoneal lesion was seen at operation or post mortem. These reports also contain a smaller number of other cases where the presence of the same lesion was suspected, but not directly observed. Nearly all the early reports were from North America, mainly from urological departments. The largest series is one of 7 cases in a paper by F. P. Raper (1956), of Leeds, who has made the important point that it may involve the main retroperitoneal vessels alone (Raper, 1955) and so should not be regarded as a urological problem exclusively. For this reason the use (*Lancet*, 1957) of the term '*peri-ureteric fibrosis*' as a general name for the disease should be dropped, and the more apt '*retroperitoneal fibrosis*' used instead.

Miller and others (1952) and Ewell and Bruskewitz (1952) suggest that the lesion is commoner than the frequency of reports would indicate. The fact that Raper has collected his cases from one centre in Great Britain in a few years supports this view.

Two further cases are reported below, one of which came to necropsy. The diagnosis, treatment, and nature of the disease will be discussed. The lesion is an important one. A recent annotation (*Lancet*, 1957) describes its pathology as "baffling in its simplicity" and says that "no primary cause can be found".

The disorder consists of a dense flattened plaque of fibrous tissue. It lies immediately anterior to the

bodies of the lumbar vertebræ and the fascia covering the front of the iliopsoas muscles. It can extend across the midline, surrounding the great vessels, or may be on one side only.

It may be confined to the level of the kidneys, or to the brim of the pelvis, or to an intermediate area. It does not extend into the mesentery to the front.

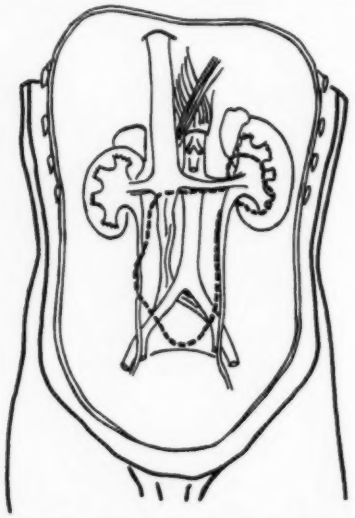


FIG. 6.—*Case* 1. The broken line shows the boundaries of the retroperitoneal fibrous plaque. Both kidneys are hydronephrotic; the right ureter is constricted for part of its course, the hilum and pelvis of the left kidney are firmly held in dense fibrous tissue, and the vena cava is constricted and for part of its course obliterated as a vessel.

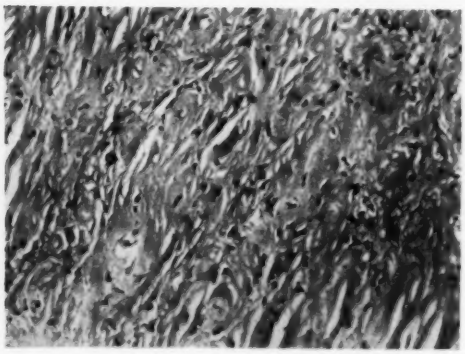


FIG. 8.—*Case* 1. Typical microscopical field showing the collagenous nature of the lesion. H. and E. (× 240.)

In its fully developed form it is up to 2 cm. thick and extends from the crura of the diaphragm above to the level of the bifurcation of the common iliac vessels below, surrounding the hila of the kidneys, bounded on the sides by lines running about a centimetre lateral to the ureters, and fading out over the brim of the pelvis.

It can (and, so far as it has been reported upon up to now, it always does) envelop and progressively constrict some or all of the structures which lie in the same site—the ureters, the aorta, the inferior vena cava, and the common iliac vessels. The histological reports are generally the same, showing the plaque to be composed of normal fibroblasts and collagen with some foci of cells of chronic inflammatory type. It has the general nature of a scar or keloid and not that of a fibroma or fibrosarcoma.

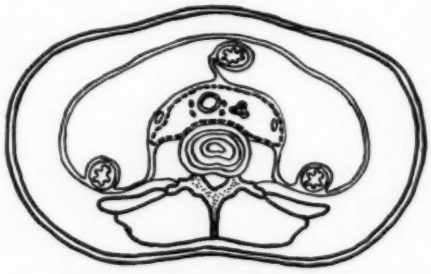
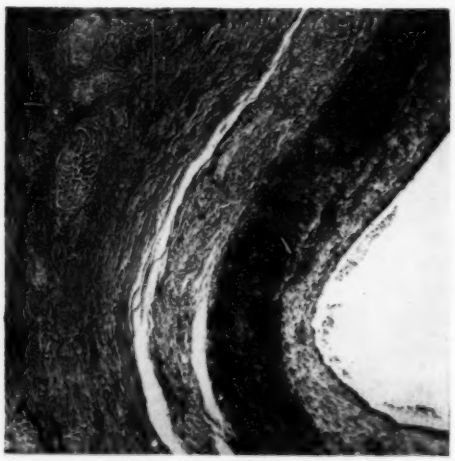


FIG. 7.—*Case* 1. The broken line shows the boundaries of the plaque in transverse section at L4. The para-aortic lymph-nodes, which were rusty-brown with hæmosiderin, are shown on either side of the aorta. (Not drawn to scale.)

The signs and symptoms provoked depend upon whether the fibrosis stiffens the pliability of the lumbar spine, reduces the blood-supply to the lower limbs by constricting the aorta or iliac arteries, embarrasses the venous return by tightening on the inferior vena cava, or causes hydronephrosis or anuria by surrounding the ureter with dense fibrous



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This is, then, a clinically recognizable condition in which surgery can be lifesaving, and which may present to the general practitioner as backache, intermittent claudication, or swelling of the lower limbs,

to the urologist as anuria or oliguria with hydronephrosis, to the vascular surgeon as an aortic, caval, or common iliac stricture, and to the pathologist as an unusual necropsy finding. Moreover, its position in the body raises problems of aetiology and anatomy.

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Of the two cases reported below, the first shows the lesion fully developed; the second is in an early or aborted stage.

Case 1.—Male, aged 40 years, motor mechanic. No previous history of serious illness or any injury. In January, 1953, he complained of pain in the small of the back radiating to the suprapubic region and both groins. It was relieved by heat and intensified by alcohol. He had then no urinary symptoms. Physical examination showed slight loss of lumbar curvature and rigidity of the lumbar spine. There was a depressed interruption in the surface line of the interspinous ligament between L_1 and L_2, suggesting an injury to the back with rupture of the ligament at some previous date, but there was no history of any such injury. X-ray examination showed no bony or joint changes in the lumbar spine.

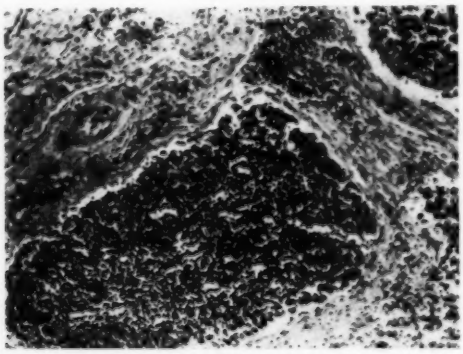

FIG. 11.—*Case* 1. Para-aortic lymph-node from left side of aorta showing dense peripheral hæmosiderin deposits which are evident without special staining for iron. H. and E. (× 64.)

Six weeks later the patient passed 'whitish' urine. In March, 1953, cystoscopy revealed a moderate cystitis, and the urine issuing from the left ureter was cloudy. The ureteric orifices were normal. A retrograde pyelogram showed slight dilatation of the pelvis of the left kidney. Blood-pressure 139/95; blood-urea 46 mg./100 c.c.; E.S.R. 15 mm. in 1 hour. Fourteen days later the blood-urea was 31 mg./100 c.c. Then his urinary symptoms cleared, leaving him 21 lb. less than his previous weight when in good health.

In November, 1953, occult blood was found in the stools and a barium meal showed a small duodenal ulcer. This healed rapidly under dietary treatment.

In August, 1956, he returned with a history of having been tired and weak for 18 months. He had a mitral systolic murmur and chest X-ray showed enlargement of the left ventricle. His brachial blood-pressure was normal, but he said that some months previously a doctor had found it to be very high. His urine was dilute (highest specific gravity 1009) and showed no albumin, casts, or red cells. His blood-urea was 320 mg./100 c.c. He complained much of tightness and pain in the region of the heart. Both legs were swollen. He became increasingly confused and died 14 days after admission.

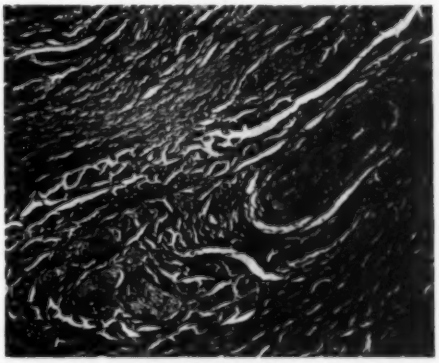

FIG. 10.—*Case* 1. A small artery and some nerves running through the collagenous plaque. H. and E. (× 64.)

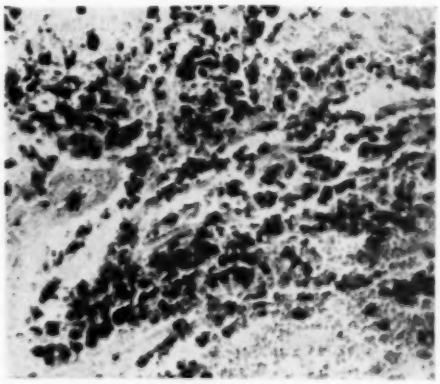

FIG. 12.—*Case* 1. Portion of lymph-node stained for hæmosiderin. Prussian blue reaction and eosin. (× 125.)

Post-mortem Examination.—Necropsy showed that the right kidney was hydronephrotic, with reduction of the parenchyma to a narrow cortical band 1 cm. in diameter. The left kidney was also hydronephrotic, but its parenchymatous tissue was normal in extent. A dense plaque of rubbery, yellowish-white tissue extended from the hila of the kidneys to the brim of the pelvis. Though it did not compress the renal vessels, it ran behind and

bodies of the lumbar vertebræ and the fascia covering the front of the iliopsoas muscles. It can extend across the midline, surrounding the great vessels, or may be on one side only.

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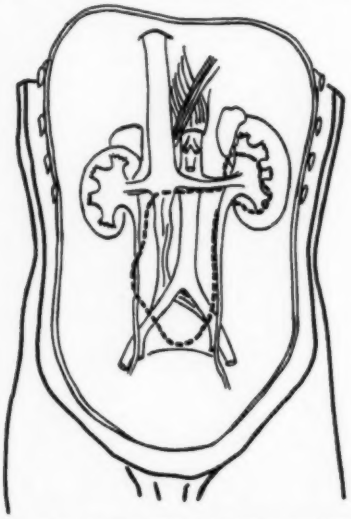

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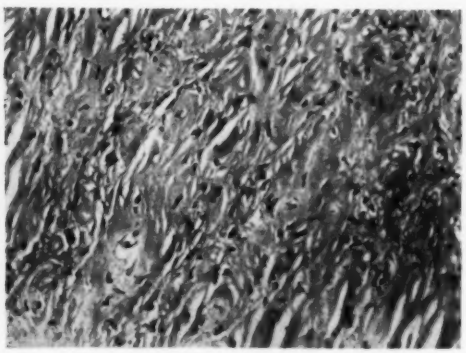

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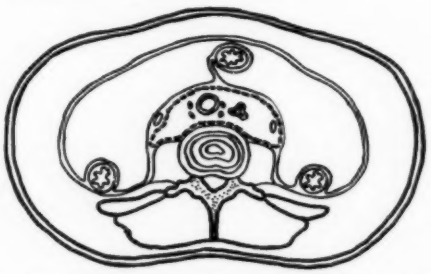

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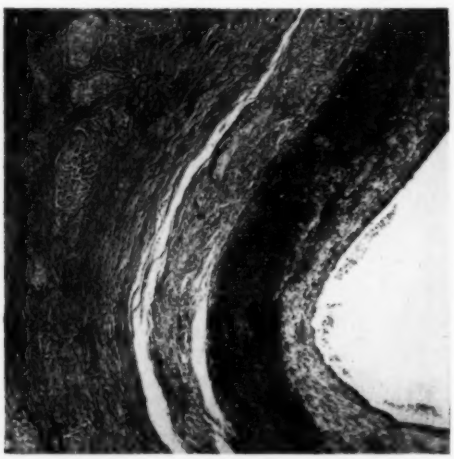

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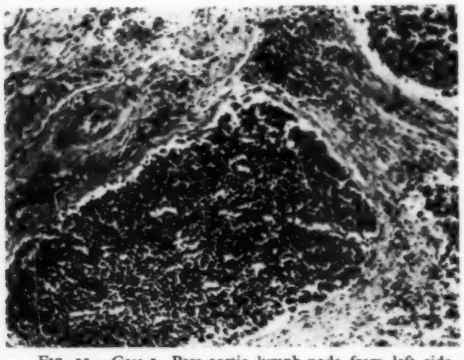


FIG. 11.—*Case* 1. Para-aortic lymph-node from left side of aorta showing dense peripheral hæmosiderin deposits which are evident without special staining for iron. H. and E. (× 64.)

Six weeks later the patient passed 'whitish' urine. In March, 1953, cystoscopy revealed a moderate cystitis, and the urine issuing from the left ureter was cloudy. The ureteric orifices were normal. A retrograde pyelogram showed slight dilatation of the pelvis of the left kidney. Blood-pressure 139/95; blood-urea 46 mg./100 c.c.; E.S.R. 15 mm. in 1 hour. Fourteen days later the blood-urea was 31 mg./100 c.c. Then his urinary symptoms cleared, leaving him 21 lb. less than his previous weight when in good health.

In November, 1953, occult blood was found in the stools and a barium meal showed a small duodenal ulcer. This healed rapidly under dietary treatment.

In August, 1956, he returned with a history of having been tired and weak for 18 months. He had a mitral systolic murmur and chest X-ray showed enlargement of the left ventricle. His brachial blood-pressure was normal, but he said that some months previously a doctor had found it to be very high. His urine was dilute (highest specific gravity 1009) and showed no albumin, casts, or red cells. His blood-urea was 320 mg./100 c.c. He complained much of tightness and pain in the region of the heart. Both legs were swollen. He became increasingly confused and died 14 days after admission.

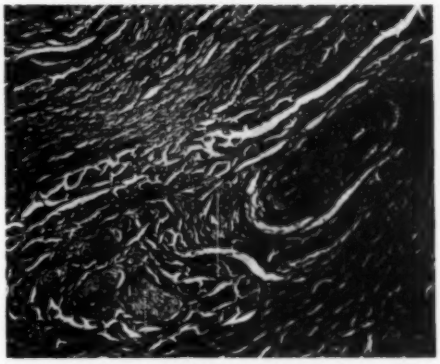


FIG. 10.—*Case* 1. A small artery and some nerves running through the collagenous plaque. H. and E. (× 64.)

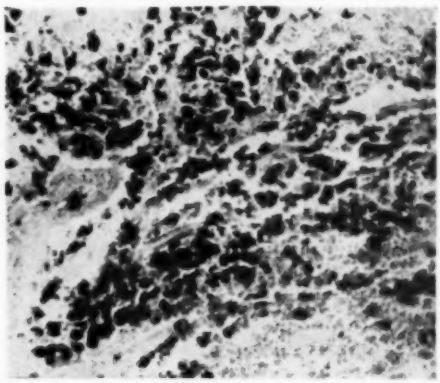


FIG. 12.—*Case* 1. Portion of lymph-node stained for hæmosiderin. Prussian blue reaction and eosin. (× 125.)

Post-mortem Examination.—Necropsy showed that the right kidney was hydronephrotic, with reduction of the parenchyma to a narrow cortical band 1 cm. in diameter. The left kidney was also hydronephrotic, but its parenchymatous tissue was normal in extent. A dense plaque of rubbery, yellowish-white tissue extended from the hila of the kidneys to the brim of the pelvis. Though it did not compress the renal vessels, it ran behind and

around the hilum and pelvis of the left kidney, enclosed the aorta and vena cava, the para-aortic lymph-nodes and nerve-chains, and the middle third of the right ureter. On the left side it ran medially to the ureter, but did not surround it. Anteriorly it was smoothly covered by peritoneum. The lumen of the aorta was 11 mm. in diameter (normal 18 mm.) where it traversed the plaque. The common iliac arteries were also covered. The aorta showed signs of atheroma or leak. The inferior vena cava was both constricted and occluded within the plaque, which ran from the beginning of each common iliac vein to a point immediately below the level of the openings of the renal veins. The fibrotic process did not extend forwards into the mesentery. Behind, it peeled cleanly from the front of the vertebral bodies (*Figs.* 6, 7).

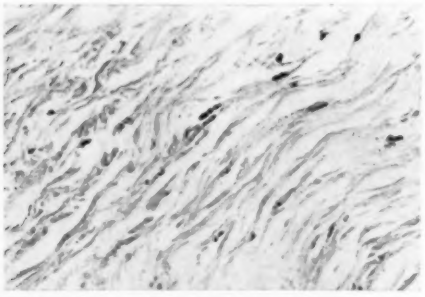


FIG. 13.—*Case* 1. Hæmosiderin distributed deep in the collagenous plaque. Prussian blue and eosin. (× 240.)

No caput Medusæ or other obvious post-mortem sign of the development of a venous collateral circulation was noted. There was concentric hypertrophy of the left ventricle, and no valvular lesions in the heart. The right lung showed slight bullous emphysema at the apex. The gastro-intestinal tract, adrenal glands, spleen, and liver showed no abnormality. Permission to open the cranium was refused. The Wassermann reaction on a specimen of heart blood was negative.

Microscopic examination showed that the tough white tissue was fibrous and collagenous throughout (*Fig.* 8). It varied from thick relatively acellular bundles of collagen to sheets of large active fibroblasts in a looser structure. The collagen was most dense along the track of the obliterated vena cava. There were occasional small foci of lymphocyte infiltration, mainly perivascular and lying towards the anterior boundary of the plaque. The tissue was well supplied with small capillaries. Both kidneys showed tubular dilatation and atrophy, as in hydronephrosis, and on both sides there was an ascending acute pyelonephritis of moderate extent. This inflammatory process did not extend to the capsules of the kidneys and there was no frank pus formation. The aorta, though enveloped by the fibrosis, could be seen in microscopic section to be separable from it (*Fig.* 9). The collagen surrounded and compressed the vessel, but did not invade it. Similarly, nerves, lymph-nodes, the right ureter, and the capsule of the left kidney all retained their integrity within the fibrous structure, being potentially separable from it by a tissue cleavage plane. But the wall of the inferior vena cava could be identified less easily. Throughout the length of the plaque it could be seen in transverse section to have a wrinkled 'ghost' outline as though it had been compressed from outside until there was occlusion, collapse, organization, and permanent obliteration of the lumen. The remnants of other similarly obliterated small veins could also be seen. The right ureter was constricted where the fibrous tissue enclosed it, but its tissue layers were intact and the wall was not invaded. The lumen was patent and the epithelial lining normal. There was peri-ureteric infiltration by lymphocytes and plasma cells.

The para-aortic lymph-nodes on both sides were rusty-brown when cut across and contained dense microscopical accumulations of hæmosiderin (*Figs.* 11, 12). Some hæmosiderin was diffusely present outside the lymph-nodes in the collagenous plaque itself (*Fig.* 13), but not in the track of the obliterated vena cava or in other parts of the body such as the liver or lungs.

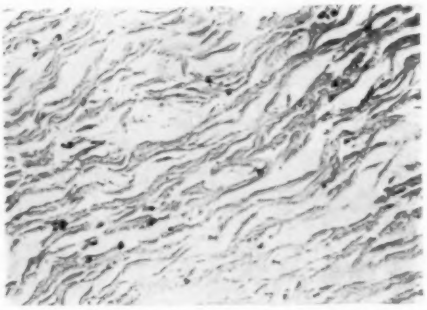


FIG. 14.—Hæmosiderin deposited in collagen from an organized subdural hæmatoma in a case of *pachymeningitis hæmorrhagica interna*. Prussian blue and eosin. (× 240.) Compare with *Fig.* 13.

Case 2.—In January, 1954, a man, aged 54 years, complained of having had pain in the small of the back for one month, testicular discomfort for three months, and loss of appetite and weight for six months. Twenty-five years previously he had had a head injury, following which he had experienced a slight pain in the back, just above the point now involved. A barium enema showed a possible obstruction in the colon and, because of this and the loss in weight, laparotomy was performed (Mr. Nigel Kinnear). This revealed colonic spasm, but no neoplasm in the intestine. There was, however, a retroperitoneal woody swelling in front of the third to the fifth lumbar vertebræ and surrounding the lower part of the aorta. A biopsy specimen cutting 1·5 cm. into the swelling was taken. The pathologist's report was: "fibrous and fatty tissue with some cellular infiltration of chronic inflammatory type. There is no evidence of malignancy" (Prof. R. A. Q. O'Meara). (Re-examination of the section in the light of the present paper shows no additional features.) An aortogram revealed narrowing of the aorta and common iliac arteries at the site of the swelling. The Wassermann reaction was negative.

The patient then went to another medical centre, where an intravenous pyelogram revealed pressure on the right ureter at the level of the fourth lumbar vertebræ with slight dilatation above. A lumbar scoliosis was noted. Irradiation totalling 4842–6000 r (min.-max.) was applied to the 'tumour' over a period of 45 days. During this time the symptoms steadily disappeared, since when, so far as is known, he has been well.

ANALYSIS OF CASES

The two cases above bring the total of those reported to 22, if we confine ourselves to those in which the lesion has been directly observed at operation or necropsy. Some useful analyses of these cases can be made:—

Sex: 16 males; 6 females. *Ages*: 5 aged 23–40 years; 15 aged 40–60 years; and 2 over 60 years. *Pain* was present in 11 cases as backache; 3 as abdominal pain; 2 as flank pain; and in 1 case as

pubic pain. There was no pain in 1 case, and the symptom was not mentioned in 4 cases. *A history of trauma* was absent in 16 cases; 4 cases had a history or evidence of injury to the abdomen, lower back, or loin; and 2 cases had had a hysterectomy for uterine leiomyomata. *Intra-abdominal inflammation* such as enteritis or colitis or cystitis was present shortly before or at the onset of symptoms in 7 cases, but was absent in 15. *Venereal disease* was clinically absent in all cases. There was no case with a positive Wassermann reaction, and in 7 cases a negative result was recorded; but the test was probably performed as part of a general investigation in most cases, though not specifically mentioned. *Brucellosis* was excluded in 2 cases. The side affected first was: left, 10; right, 7; both together, 3; and in 2 cases this point was not made clear. The lesion when seen at operation or autopsy was *bilateral* in 17 cases, *right-sided* in 3, and *left-sided* in 2. In 3 cases the lesion was placed low and affected the brim of the pelvis only—in 1 being bilateral and affecting the bifurcation of the aorta and both common iliac arteries, while in 2 it was on the right side affecting only the right common iliac. In some of the cases investigated entirely from a urological viewpoint, it is possible that the great vessels were to some extent involved as well as the ureters. It is clear that in any case of unexplained ureteric block it is worth comparing the brachial with the femoral pulse, and looking for engorgement in the superficial veins of the abdomen.

Raper (1956) points out as an important feature of the disease that a ureteric catheter may sometimes be passed through an affected ureter without detecting any obstruction. The apparent absence of a block may be misleading, but Raper ascribes this to the fact that peristalsis and therefore urinary flow may be deficient in a ureter which is firmly surrounded by fibrous tissue, but not tightly compressed.

Surgical treatment or laparotomy was carried out in all except 1 case. In 12 cases successful dissection to free the ureter(s) or kidney was carried out; in 3 cases treatment was by nephrostomy only; there were 2 nephrectomies, and 4 diagnostic laparotomies.

Other treatment: 3 cases were irradiated. The doses were 600 r (Oppenheimer and others, 1952), 840 r (Bradfield, 1953), and 4842–6000 r (*Case* 2 here reported). There was apparent improvement in the first and third of these cases, but no improvement or histological change in the second case.

There is no record of treatment with cortisone.

Autopsies: 3 cases came to necropsy (Ormond, 1948; Raper, 1956; and *Case* 1 described in this paper).

DISCUSSION

The Anatomy of the Site.—The boundaries within which this disorder occurs are very definite. In only one instance (Raper, 1956, *Case* 7) has it been seen extending above the hila of the kidneys, and then it was a midline extension ascending around the aorta, passing up between the crura of the diaphragm and over slightly to the right to involve the lower end of the common bile-duct. Laterally, the lesion does not pass a line running 1 cm. on the lateral side of the ureters. Below, it stops at the pelvic brim. In no case has it extended anteriorly into the mesentery or around the cœliac or mesenteric arteries. These limited boundaries correspond to those of the renal fascial compartments.

The classical text-book description of the renal fascia is that it consists of anterior and posterior layers which closely enclose the kidney and usually the suprarenal gland superiorly, and fuse immediately above this to become continuous with the fascia under the diaphragm. Below the kidneys the two layers remain apart and continue downwards as twin membranes enclosing the ureters. Laterally the layers blend together and merge with the retroperitoneal connective tissue over the psoas and quadratus muscles. Below, they fuse similarly over the brim of the pelvis, merging with the extra-peritoneal tissue lining the iliac fossa. However, the anterior and posterior layers are classically described as extending as continuous sheets in front and behind the great vessels, so that in effect both ureters, both kidneys, and the blood-vessels are all in one single fascial compartment. Whether or not this is so is of some importance in the present discussion.

Certain anatomists (Southam, 1923; Mitchell, 1950) have dissented from the classical description and have stated that both anterior and posterior layers of the renal fascia fuse firmly with the peri-aortic and pericaval connective tissue in the midline, thus making distinct right and left compartments. If this is so, it means that a pathological process which has a tendency to be confined to fascial compartments (as this one has) would, if it originated in or around the ureter, be usually unilateral and would not extend to the other side (unless by chance it started separately on both sides at the same time). But if it began in the central line of connective tissue it might be expected to spread bilaterally. We have already noted that in 17 of the 22 reported cases this idiopathic retroperitoneal fibrosis has been bilateral.

Mitchell (1950), in a most convincing paper, demonstrates that the central partition of the renal fascial compartment is a reality. He says that distinct layers of renal fascia either anterior or posterior to the aorta and inferior vena cava "can be created only by artificial dissection of the surrounding connective tissue". The separation of anatomical layers and the demonstration of fusion between plaques of connective tissue is of course influenced by the delicacy of the technique used to dissect them. But by injecting radio-opaque fluid under measured pressure and watching the sequence of its spread, Mitchell shows that the medial partition is a firm one and that if it has any relative weakness it is below, at the iliolumbar region. Chisholm and others (1954) reported a case of this disorder which involved both ureters. Seeking to explain its nature they quote Daseler and Anson (1943), who have made an anatomical study of the renal fascia in a case with bilateral ectopic iliolumbar kidneys. These workers found that there was a single renal fascial compartment with no medial partition in their case and came to a general conclusion that "whether the kidney be normal or ectopic the investment remains the same". Such a general anatomical conclusion seems unwise when based on the examination of an abnormal case. Mitchell's conclusions are better founded.

With this matter in mind, I have inspected the renal fascia at 10 successive general necropsies on adults. I found that in the fresh unfixed specimen the renal fascia can be seen to blend quite firmly with the peri-aortic and loosely with the pericaval connective tissue, but that separation of the anterior layer by firm blunt dissection is quite feasible in some cases and displays a clear continuous membrane. The fascia behind the vessels, however, is very firmly adherent to them. As far as I can see there is a definite, but not absolute, barrier dividing the renal into right and left compartments.

Aetiology of the Disease.—So far, no satisfactory cause has been proposed. In comparison, there are some well-known diseases which are idiopathic and fibrosing and occur in characteristic local sites.

For example, *keloids* are hypertrophic cutaneous scars which develop as a reaction to burns, incisions, trauma, or other stimuli in negroes and others who have an individual predisposition to this reaction. Histologically, the keloid has much in common with the retroperitoneal lesion discussed here.

Dupuytren's contracture of the palmar fascia, *Mondor's disease* of a vein in the breast (Lunn and Potter, 1954; Kaufman, 1956), and *Peyronie's disease* of the dorsum of the penis are other examples of puzzling local fibrotic changes. It is hard to see anything in common between them, unless it be a vascular disorder.

Ischæmia will promote fibrosis, but only in existing tissue where the blood-supply is reduced—it will not cause the proliferation of fibroblasts and the production of collagen in a space normally unoccupied, which is what happens in this idiopathic retroperitoneal fibrosis.

Syphilis is the great cause of fibrosis in unexpected sites, but in all the cases reviewed here there was no history of it, and serological examination excluded it in at least some. Besides, the histological picture of syphilis, though often confusing is, likewise, often recognizable and would certainly be evident in some of 22 cases.

A leak of irritant or infective material from kidneys or ureter ought to involve these organs in any inflammatory or fibrotic process produced. There would be a ureteritis, for instance, involving all coats, matting the ureter to the surrounding collagen in a peri-ureteritis and not leaving it merely in a state of peri-ureteric fibrosis. Indeed it is precisely this non-involvement of the walls of the ureters and vessels which makes any inflammatory aetiology so unlikely.

Such pyelonephritis as can be seen histologically in the necropsy case reported in this paper is minimal and more readily explained as an accompaniment of hydronephrosis than as part of the obstructive process which caused it.

A benign neoplasia of fibroblasts or fibrocytes develops as a solid rounded fibroma and not as a diffuse growth. Nevertheless, one might perhaps conjecture that a mesenchymal cell like the fibroblast, the nature of which is to move and migrate in the tissue spaces, might exhibit a local type of diffusely growing benign or near-benign neoplastic change. If there is such a lesion it is a keloid, and keloid is confined to the skin. If, here, we are dealing with 'keloid of the renal fascial compartment' it is hard to see why it should not occur in other sites too—in fascial planes in the muscles, around the joints, in the mediastinum, and so on. But it does not do so.

The primitive embryonic mesenchyme develops in this region. It is just possible that its fibroblasts could retain some special atavistic quality which would allow them to proliferate in an abnormal or special manner. But there is no evidence at all to support such an aetiology.

Oberling (1935) describes 6 cases of 'retroperitoneal xanthogranuloma' or 'fibroxanthoma'. This lesion is abundantly fibrocytic, but is also infiltrated by foam cells containing cholesterol, cholesterol esters, and neutral fats, and occupies the retroperitoneal tissues outside the renal fascial envelope. It is a disease of the Hand-Schüller-Christian type, but the unusual amount of fibrosis perhaps indicates a special propensity for fibroblast activity in the retroperitoneal locality.

Now in what other way can simple fibrosis come about? And how may it be promoted in this unusual enveloping manner, as though it had flowed around the structures of the renal fascial space like a liquid which then set to a firm gel? These questions have one answer—fibrin. Fibrin could be deposited in the renal fascial space in just this way by hæmatoma formation. If not absorbed, it would be invaded by fibroblasts and the resultant organization would be in the form of an enveloping scar.

The renal fascial space is loose and not massaged by surrounding muscles. In fact a lax abdominal wall might even leave it in an occasional state of negative pressure while the body was erect. It is a place from which blood or a fibrinous effusion might not be removed readily by ordinary physiological drainage processes, and thus would become slowly organized to collagenous tissue.

I believe that in the necropsy case reported in this paper, the dense hæmosiderin in the para-aortic abdominal lymph-nodes on both sides and the enveloping nature and extent of the lesion strongly suggest that it is the result of past bleeding—an organized hæmatoma. Bleeding may have been arterial or venous, perhaps from a very small vessel in the midline connective tissue. It may have been caused by an injury so long ago that the history is forgotten—even by a birth injury. Steady organization and contraction in the following years would do the rest.

Idiopathic retroperitoneal fibrosis usually takes some years to develop fully, though sometimes the symptoms may be excited rapidly by intervening infection or operation. Only 4 of the cases reviewed here had a history of trauma, but in one of them MacLean (1954) suggests that the lesion is the result of a hæmatoma produced by an injury which occurred twenty-one years previously. In none of them is there any mention of hæmosiderin deposition, or of the state of the lymph-nodes. However, a fibrinous effusion from injured or irritated retroperitoneal central perivascular tissue might even produce the same final effect without release of hæmosiderin.

It is instructive to compare *pachymeningitis hæmorrhagica interna* as an example of a lesion where the histological appearances can be strikingly similar

to those of the one under discussion. It is caused by a leak of blood between the dura and the arachnoid mater. A hæmatoma forms, in which there can be no development of lymphatic drainage by which insoluble products may be removed. Then the organization of the fibrin to dense collagen with hæmosiderin deposition is a characteristic consequence, the lesion being one of repair, rather than of inflammation as implied in the name pachymeningitis. (Compare *Figs.* 13 and 14.)

Collagenous replacement of fibrin: this is a simple explanation of '*idiopathic retroperitoneal fibrosis*', but it is reasonable and may be the process involved in most, if not all, the cases of this condition.

Treatment.—Consideration of the reported cases leads to the conclusion that the best treatment has been surgical.

The fibrous tissue is slowly, but steadily, contracting. If the patient lives long enough it may eventually obliterate any of the tubes it surrounds. Ureters have been successfully lifted out of the fibrous bed and can, if necessary, be brought within the peritoneal cavity to prevent further involvement. Freeing the vena cava could similarly be attempted, though its wall is thin. The aorta cannot be dissected away from its lumbar arteries, but in the case of both vessels a stripping of the dense collagen vertically from the front ought to give relief.

Irradiation is unlikely to have any effect on dense collagenous tissue. Its use in some reported cases is presumably due to the progressive and spreading nature of the lesion suggesting a neoplastic process—in spite of the pathologists' reports on biopsy specimens. The period of rest in bed while such treatment was being given may itself have contributed to the improvement noted after radiation in 2 cases, for it would have relieved the circulation to the lower limbs and prevented gravitational drag on a potentially hydronephrotic kidney.

Raper (1956) and others (Case Records of the Massachusetts General Hospital, 1957) mention the possibility of treatment with cortisone. It was not used in any of the cases reviewed. In the 2 cases reported in this paper the fibrous tissue seen in the sections is so dense that it is most unlikely that cortisone treatment would have been effective.

SUMMARY

1. The condition becoming known as 'idiopathic retroperitoneal fibrosis' is described, and 20 cases previously published are reviewed.

2. Two further cases are reported, with the necropsy findings in one of them.

3. The nature of the lesion is discussed and the opinion expressed that in some, and perhaps most, cases it is produced by organization of a hæmatoma or of a fibrinous effusion.

4. The treatment should be surgical.

I am grateful to Prof. R. A. Q. O'Meara for good advice in the evaluation of this condition, and for allowing me to quote his histological report on *Case* 2.

I also thank Mr. Nigel Kinnear and Mr. John Sugars, of the Adelaide Hospital, Dublin, for allowing me to examine their clinical notes on *Cases* 1 and 2; and Mr. Dermot O'Flynn, of the Genito-Urinary Surgical Unit of the Meath Hospital, Dublin, who first told me about this disease.

REFERENCES

AMSELEM, A. (1950), *Med. esp.*, **23**, 230.
BRADFIELD, E. O. (1953), *J. Urol.*, **69**, 769.
Case Records of the Massachusetts General Hospital (Case 42281) (1956), *New Engl. J. Med.*, **255**, 90.
Case Records of the Massachusetts General Hospital (Case 43252) (1957), *Ibid.*, **256**, 1198.
CHISHOLM, E., HUTCH, J. A., and BOLOMEY, A. (1954), *J. Urol.*, **72**, 812.
DASELER, E. H., and ANSON, B. J. (1943), *J. Urol.*, **49**, 789.
EWELL, G. H., and BRUSKEWITZ, H. W. (1952), *Urol. cutan. Rev.*, **56**, 3.
KAUFMAN, P. A. (1956), *Ann. Surg.*, **144**, 847.
Lancet (1957), **2**, 780.
LUNN, G. M., and POTTER, J. M. (1954), *Brit. med. J.*, **1**, 1074.
MACLEAN, J. T. (1954), *Brit. J. Urol.*, **26**, 127, 230.
MILLER, J. M., LIPIN, R. J., MEISEL, H. J., and LONG, P. H. (1952), *J. Urol.*, **68**, 447.
MIRABILE, C. S., and SPILLANE, R. J. (1955), *Ibid.*, **73**, 783.
MITCHELL, G. A. G. (1950), *Brit. J. Surg.*, **37**, 257.
OBERLING, C. (1935), *Amer. J. Cancer*, **23**, 477.
OPPENHEIMER, G. D., NARINS, L., and SIMON, N. (1952), *J. Urol.*, **67**, 476.
ORMOND, J. K. (1948), *Ibid.*, **59**, 1072.
RAPER, F. P. (1955), *Proc. R. Soc. Med.*, **48**, 736.
— — (1956), *Brit. J. Urol.*, **28**, 436.
SOUTHAM, A. H. (1923), *Quart. J. Med.*, **64**, 283.

THE URINARY EXCRETION OF CALCIUM AND INORGANIC PHOSPHATE IN 344 PATIENTS WITH CALCIUM STONE OF RENAL ORIGIN

By A. HODGKINSON and L. N. PYRAH

FROM THE METABOLIC DISTURBANCES IN SURGERY M.R.C. UNIT, THE GENERAL INFIRMARY AT LEEDS

Introduction.—The term 'calcium stone of renal origin' is used here to describe stones which have been found in the kidney or have apparently originated in the kidney, and which consist wholly or partly of calcium salts.

Flocks (1939) observed that the urinary excretion of calcium is high in many patients with stones of this type. In a study of 35 patients (22 men and 13 women) he found that 21 (60 per cent) excreted more than 200 mg. calcium per day when on a moderately low intake of 300 mg. calcium per day, whereas only 1 of 12 normal individuals on the same intake excreted more than 200 mg. per day. In a similar study of 26 patients on a low calcium diet, Sutherland (1954) found that 15 (58 per cent) excreted more than 200 mg. calcium per day. Cottet and Vittu (1955), comparing 52 calcium stone patients with 56 normal individuals on a normal mixed diet, found that the average daily excretion of calcium exceeded 200 mg. in 75 per cent of the stone patients, compared with 31 per cent of the normal individuals. They also found that the incidence of high urine-calcium values varied with the type of stone, but they could find no significant difference in phosphate excretion between normal individuals and stone patients. McGeown and Bull (1957) found that on a diet containing 154 mg. calcium per day, the urinary excretion of calcium by normal individuals was within the range 48–148 mg. per day (mean 83 mg., S.D. 32 mg.). In a series of 73 stone patients they found that 30 per cent had values greater than the mean plus twice the standard deviation.

The studies described above were made on comparatively small groups and it appeared desirable to examine larger groups of normal individuals and stone patients. The present survey is based on data from various sources, on 258 normal adults, and on studies on 344 patients with calcium stone of renal origin who presented at the Leeds Clinic in recent years. It is considered that these 344 patients are a fairly representative sample of the stone patients presenting at this clinic, but they may not be representative of stone cases in general since stones may be passed in the urine after minimal symptoms and such individuals may not present at the clinic.

The investigation on each of the 344 stone patients included the determination of calcium and inorganic phosphate in several 24-hour samples of urine, with the patient on a normal diet, and the determination of serum-calcium, inorganic phosphate, protein, urea, chloride, alkaline phosphatase, and carbon-dioxide combining power. Additional investigations on some of the patients included the determination of urinary calcium on a low calcium diet, the estimation of renal function by urea or inulin clearance or intravenous pyelogram, the chemical and crystallographic analyses of stones, and the histological examination of renal tissue.

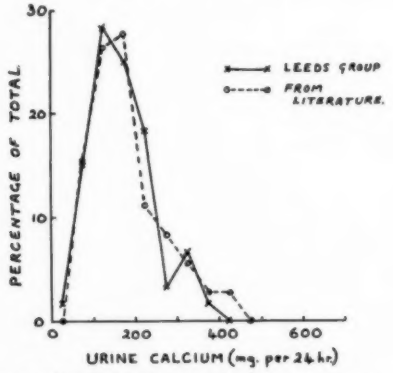


FIG. 15.—The distribution of urine-calcium values for two groups of normal men on normal diet.

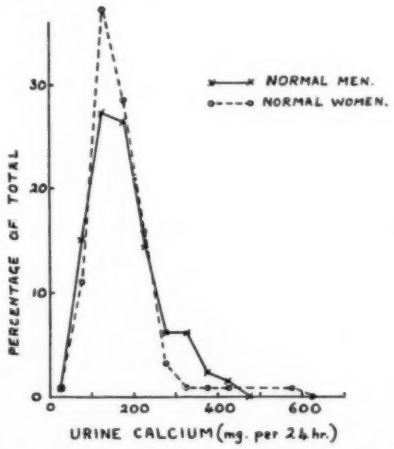


FIG. 16.—The distribution of urine-calcium values for 132 normal men and 126 normal women on normal diet.

The excretion of urine-calcium and inorganic phosphate in relation to diet, renal function, sex, type of stone, and other factors is considered and some observations are made on the significance of high calcium excretion in relation to calcium stone formation.

The Urinary Excretion of Calcium by Healthy Adults on Normal Diet.—Knapp (1947) concluded from a survey of 600 normal men, women, and children that the urinary excretion of calcium depends on the intake of calcium per unit body-weight and on an endogenous factor or factors characteristic of the individual. Age and sex are not factors except as they affect body-weight.

We have found from an examination of this and other published data that the effect of moderate variations in body-weight and calcium intake on the urinary excretion of calcium is small compared with the effect of physiological variations between individuals. The intake of calcium on our normal ward diet is estimated to be within the range 800 ± 200 mg. per day, and it may be noted that the calcium content of adult diets does not, in general, appreciably exceed this range unless there is an excessive intake of milk or milk foods. The effect of variations in calcium intake on the urinary excretion of calcium by normal individuals may be calculated using the equations proposed by Knapp (1947). For intakes within the range 800 ± 200 mg. per day the variation is less than ±6 per cent. Using the same equations it is found that a difference of 1 st. (6·3 kg.) in body-weight corresponds to a difference of 8 per cent in the average excretion of calcium. In contrast, the range of urine-calcium values for normal adults weighing 70 kg. on an intake of 800 mg. calcium per day is 36–416 mg. per day, with an average value of 181 mg. Such a wide range is of little value for diagnostic purposes, and it is of interest to determine the distribution of values for a group of normal adults on an intake within the range 800 ± 200 mg. calcium per day. Men and women are considered separately in order to minimize the effect of body-weight. The distribution of average urine-calcium values for 60 non-stone patients convalescing on normal ward diet after minor surgical treatment at St. James's Hospital, Leeds, is given in *Fig.* 15. In order to determine whether this distribution is representative of normal adult men, additional data for 72 normal adult men on an intake of 800 ± 200 mg. calcium per day were obtained by reference to the following literature: Breiter, Mills, Dwight, McKey, Armstrong, and Outhouse (1941); Hegsted, Moscoso, and Collazos (1952); McCance and Widdowson (1939, 1942); McCance, Widdowson, and Lehman (1942); McClellan, Rupp, and Toscani (1930); Malm (1953); Nicolaysen, Eeg-Larsen, and Malm (1953); Owen, Irving, and Lyall (1940); Steggerda and Mitchell (1939, 1941, 1946, 1951); Striebel and Viollier (1949).

The differences between the Leeds group and the group obtained from the literature are considered to be no greater than those to be expected from sampling error, and in *Fig.* 16 these two groups are treated as a single entity. *Fig.* 16 also shows the distribution of average urine-calcium values for a group of 126 normal adult women on an intake within the range 800 ± 200 mg. calcium per day. The data for this group were obtained by reference to the following literature: Blatherwick and Long (1922); Bogert and McKittrick (1922 a, b); Breiter and others (1941); Bricker, Smith, Hamilton, and Mitchell (1949); Hunscher, Donelson, Erickson, and Macy (1934); Leverton and Marsh (1942); McCance and Widdowson (1942); and Pittman and Kunerth (1939).

Table I.—THE INCIDENCE OF HIGH URINE-CALCIUM VALUES IN NORMAL ADULTS AND IN STONE PATIENTS

Average Urine-calcium on Normal Diet (mg. per 24 hr.)	Percentage of Total					
	Men and Women		*Men*		*Women*	
	258 Normal Individuals	344 Stone Patients	132 Normal Men	220 Male Stone Patients	126 Normal Women	124 Female Stone Patients
Greater than 200	26	52 (59)*	30	61 (65)	22	36 (44)
" " 250	11	40 (45)	16	49 (52)	6	25 (31)
" " 300	7	28 (30)	10	35 (37)	3	11 (14)
" " 350	3	15 (17)	4	21 (22)	2	6 (7)
" " 400	1·5	9 (10)	2	13 (14)	1	2 (3)

* Figures in brackets denote percentages after omitting patients with evidence of poor renal function.

The majority of men and women excrete between 100 and 200 mg. calcium per day, but the distributions in each case are asymmetrical and a few individuals in each group excrete exceptionally large amounts of calcium. As shown in *Table I*, the incidence of high urine-calcium values is greater in normal men than in normal women.

The Relationship between Renal Function and the Urinary Excretion of Calcium.—It was observed in the course of this study that patients with marked impairment of renal function had a low urinary excretion of calcium, and a definite pattern was obtained on plotting the available urea clearances for stone patients against the corresponding urinary calcium values on normal diet (*Fig.* 17).

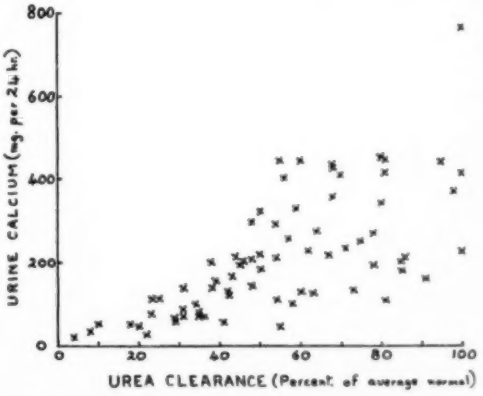


FIG. 17.—The relationship between the urinary excretion of calcium on normal diet and the clearance of urea (72 cases).

The results suggest that the daily excretion of calcium on normal diet does not exceed 150–200 mg. per day if there is less than 40 per cent of normal

glomerular function. It may be observed in this connexion that Flocks (1939) found evidence of only slight pathological changes in the kidneys of stone patients with hypercalciuria whereas marked pathological changes were usually associated with a definitely lowered urine-calcium.

These observations suggest that in any group of stone patients, the proportion having high urine-calcium values will depend, in part, on the number of patients having poor renal function, and we have examined the records of our stone patients with a view to assessing the proportion with poor renal function. The most satisfactory criterion for this purpose is the clearance of inulin or urea, and this information was available for 75 of our 344 patients. For the remainder, renal function was assessed on the basis of the blood-urea level and the intravenous pyelogram. In the present context renal function was considered to be 'poor' if the urea clearance was less than 40 per cent of average normal, or if the blood-urea nitrogen was greater than 30 mg. per cent, or the intravenous pyelogram showed fair or poor excretion of dye. Using these criteria it was found that there was evidence of poor renal function in 14 of the 220 male stone patients (6·4 per cent), and 24 of the 124 female stone patients (19·3 per cent). It is realized that the blood-urea level and intravenous pyelogram are not very sensitive measures of renal function and it is possible that a few patients with poor renal function may have been missed. We consider, however, that the true incidence of poor renal function among our stone patients is probably not greater than 10 per cent of men and 25 per cent of women.

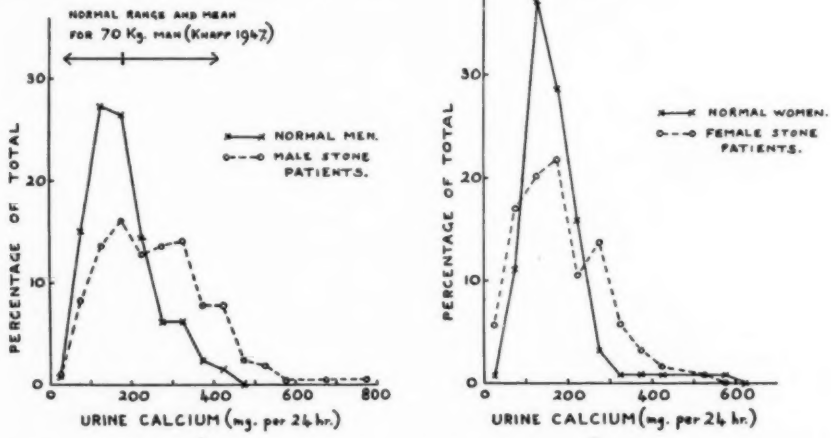


FIG. 18.—A, The distribution of urine-calcium values for normal men and 220 male stone patients on normal diet. B, The distribution of urine-calcium values for normal women and 124 female stone patients on normal diet.

The relationship between renal function and the urinary excretion of inorganic phosphate is less well defined, but phosphate excretion appears to be depressed when the urea clearance is less than 20 per cent of normal.

Comparison of Calcium Excretion by Normal Adults and Stone Patients on Normal Diet.—In *Fig.* 18 A the distribution of urine-calcium values for normal men may be compared with that for a group of 220 male stone patients, and in *Fig.* 18 B the distribution of values for normal women may be compared with that for 124 female stone patients. The incidence of high urine-calcium values in normal adults and in stone patients is given in *Table I.*

From this survey it was found that the incidence of high urine-calcium values is greater in normal men than in normal women. Similarly, the incidence is higher in male stone patients than in female stone patients.

The percentage of normal individuals and stone patients with average urine-calcium values greater than 200 mg. per day were 26 and 59 respectively, compared with values of 31 and 73 reported by Cottet and Vittu (1955).

The Urinary Excretion of Calcium on Normal and Low Calcium Diets.—Nicolaysen, Eeg-Larsen, and Malm (1953), describing a long-term study of calcium and phosphorus metabolism in 19 normal men, observed that halving the calcium intake (from 900 to 450 mg. per day) resulted, in most cases, in a small decrease in the urinary excretion of calcium. In some cases, however, there was no appreciable change, or even a small increase. In one case with an exceptionally high excretion there was a decrease from 418 to 276 mg. per day.

The urinary excretion of calcium on normal ward diet (800 $\pm$ 200 mg. calcium per day) and on a low-calcium diet (130–170 mg. calcium per day) was studied in 32 patients from the present series, and the results are illustrated in *Fig.* 19. The values on the left-hand side are the mean of several 24-hour collections made on the higher calcium intake, while the values on the right-hand side are the mean of three 24-hour collections made in the latter half of a six-day period on the low-calcium diet. The corresponding points for each individual are joined by

solid or dotted lines, the latter denoting proved cases of hyperparathyroidism. In general, the picture is similar to that described by Nicolaysen and others (1953) for normal individuals.

According to the equations proposed by Knapp (1947) the upper limit of calcium excretion for normal

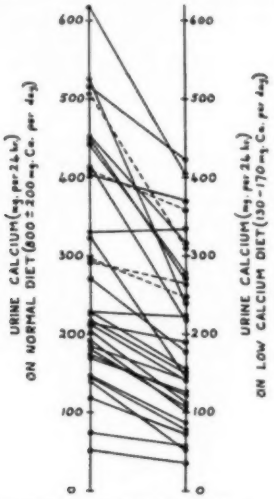

URINE CALCIUM (mg. per 24 hr.) ON NORMAL DIET (600 = 200 mg. Ca. per day)
URINE CALCIUM (mg. per 24 hr.) ON LOW CALCIUM DIET (130 - 170 mg. Ca. per day)
600
500
400
300
200
100
0

FIG. 19.—The urinary excretion of calcium by 32 stone patients on normal and low calcium diet.

We have concluded from a survey of the literature that on an intake of 150 mg. calcium per day, at least 90 per cent of normal adults excrete less than 175 mg. calcium per day. In the series of 32 patients considered here, 16 had a urine-calcium value greater than 175 mg.

The upper limit of normal calcium excretion on normal diet cannot be defined precisely but 90 per cent of normal men excrete less than 300 mg. calcium per day and at least 90 per cent of women excrete less than 250 mg. calcium per day. If these values are taken as the approximate upper limits of normal, then 14 of the 32 patients quoted had abnormally high urine-calcium values. This figure is in reasonable agreement with that obtained on low-calcium diet.

It should be pointed out that the 32 cases quoted above are not a representative selection of stone patients, but they serve to show that in most cases an abnormality of calcium excretion may be detected as readily on a normal diet as on a carefully controlled low-calcium diet. This point may be of practical value in situations where an assessment of calcium excretion is required but where a strict control of dietary intake is not practicable. Measurements on accurately controlled intake are, of course, to be preferred where this is practicable.

The Relationship between Urinary Excretion of Calcium and Type of Stone.—Cottet and Vittu (1955) divided a group of 52 calcium-stone cases into three categories according to the type of stone found on analysis. The proportion in each group which had urinary calcium values in excess of 200 mg. per day was compared with the proportion in a group of 56 normal individuals on a similar normal diet.

Table II.—THE RELATIONSHIP BETWEEN THE URINARY EXCRETION OF CALCIUM AND THE TYPE OF STONE

GROUP	LEEDS SERIES		COTTET AND VITTU (1955)	
	Number of Individuals	Urine-calcium (Percentage with values greater than 200 mg. per day)	Number of Cases	Urine-calcium (Percentage with values greater than 200 mg. per day)
Men and Women:—				
Normal adults	258	26	56	31
Calcium-phosphate stones	13	23 (30)†	11	54
Calcium-oxalate stones	50	50 (53)	26	69
Mixed calcium-oxalate and calcium-phosphate stones	58	67 (77)	15	93
Mixed struvite* and calcium-phosphate stones	17	12 (17)	—	—
Men:—				
Normal men	132	30		
Calcium-phosphate stones	5	60 (60)		
Calcium-oxalate stones	41	51 (55)		
Mixed calcium-oxalate and calcium-phosphate stones	38	79 (91)		
Mixed struvite and calcium-phosphate stones	7	Nil (Nil)		
Women:—				
Normal women	126	22		
Calcium-phosphate stones	8	Nil (Nil)		
Calcium-oxalate stones	9	44 (44)		
Mixed calcium-oxalate and calcium-phosphate stones	20	45 (53)		
Mixed struvite and calcium-phosphate stones	10	20 (25)		

* Struvite = Magnesium ammonium phosphate hexahydrate.
† Figures in brackets denote percentages after omitting patients with evidence of poor renal function.

adults on the low-calcium diet is approximately 290 mg. per day. Albright and Reifenstein (1948) considered the upper limit to be about 150 mg. per day on an intake of approximately 137 mg. calcium per day.

Analysis of stones has been carried out in 136 cases in the present series, and the findings from the two series are summarized in *Table II*. In the upper part of the table, men and women from our series are grouped together in order to make our results comparable with those reported by Cottet and Vittu. In the present case it was found necessary to add a fourth group consisting of patients having mixed struvite–calcium-phosphate stones.

Considering men and women together, the incidence of high urine-calcium values increases in the following order: mixed struvite–calcium-phosphate stones, calcium-phosphate stones, calcium-oxalate stones, mixed calcium-oxalate–calcium-phosphate stones. In the group of patients with mixed struvite–calcium-phosphate stones the incidence of high calcium values is lower than in normal adults. This discrepancy is probably due to sampling error.

Our findings are in general agreement with those of Cottet and Vittu (1955), but the incidence of high calcium values in each group in our series is lower than that in the corresponding group reported by Cottet and Vittu. This difference is still appreciable after omitting the patients with poor renal function from our series (*see* figures in brackets).

With one exception the order of incidence of high calcium values remains the same if male and female stone patients are considered separately. The one exception, calcium-phosphate stones in men, is probably due to sampling error since there were only 5 patients in this group. The incidence of high calcium values in each group of men tends to be higher than in the corresponding group of women. This difference may be due in part to differences in skeletal weight since the urinary excretion of calcium is related to the latter (Knapp, 1947).

It is concluded that in patients with calcium-phosphate or mixed struvite–calcium-phosphate stones the incidence of high urine-calcium values is approximately the same as in normal adults. In the majority of such cases it would appear that hypercalciuria is not an important contributory factor and treatment is generally directed towards removing the infection and producing an acid urine. In contrast, 66 per cent of patients with oxalate or mixed oxalate–phosphate stones had average urine-calcium values greater than 200 mg. per day compared with 26 per cent of normal individuals. In these cases it would appear that hypercalciuria is an important contributory factor.

B. Murphy (private communication of results to be incorporated in a thesis) has suggested an alternative classification of calcium-oxalate-containing stones, based on structure rather than on chemical composition. He concluded from an examination of a large number of stones in thin section in the polarizing microscope that amorphous material or 'colloid' is present in all calcium stones of renal origin. In some stones (Type I) the colloid appears to determine the structure of the stone, whereas in others (Type II) the colloid appears merely to fill the interstices of a mass of crystals. Murphy has suggested that these two types of structure may arise as a result of different mechanisms. Thus, the formation of stones of Type I would appear to depend on the presence of the colloid rather than on simple crystallization from solution, whereas the reverse would appear to hold for stones of Type II. If this hypothesis is correct then it might be expected that the urinary excretion of calcium would be higher in patients with stones of Type II than in those with stones of Type I.

Calcium-oxalate-containing stones from 74 patients have been classified on the basis of their structure, and it was found that 28 were of Type I while the remainder were of Type II. Seven of the 74 patients had poor renal function, and after omitting these it was found that the urinary excretion of calcium exceeded 200 mg. per day in 71 per cent of the patients with stones of Type II compared with 32 per cent of the patients with stones of Type I and 26 per cent of normal adults (*see Table II*).

In view of the many factors other than the concentration of calcium which affect the solubility of calcium-oxalate in urine, these results are in satisfactory agreement with the above hypothesis. The series of cases investigated is at present too small to determine whether the agreement is fortuitous and further data are being collected.

The Urinary Excretion of Calcium in relation to Other Possible Contributory Factors in Stone Formation.—Parathyroid adenoma or hypertrophy was found at neck exploration in 8 of the 344 stone patients under review. In a further 16 cases there was evidence of an anatomical abnormality of the kidney, and 23 patients in the series had a family history of renal stone. In 17 cases there was evidence of prolonged recumbency at some time prior to admission for treatment for kidney stone. The urinary excretion of calcium is raised during periods of immobilization, but excretion generally falls when activity is resumed (Deitrick, Whedon, and Shorr, 1948; Cordonier and Talbot, 1948). A histological examination of renal tissue from 40 patients in the series revealed evidence of chronic pyelonephritis in 21 cases.

The incidence of high urine-calcium values in each of the above groups is given in *Table III*.

Table III.—The Urinary Excretion of Calcium in Relation to Other Possible Contributory Factors in Stone Formation

Group	Number of Patients	Percentage with Urine-calcium Values greater than 200 mg. per Day
Primary hyperparathyroidism	8	87 (100)*
Family history of renal stone	23	57 (59)
Prolonged recumbency	17	41 (54)
Anatomical abnormality of kidneys	16	37 (46)
Chronic pyelonephritis	21	24 (31)

* The figures in brackets denote percentages after omitting those patients having evidence of poor renal function.

From the data contained in *Tables I* and *III* it is concluded that the incidence of high urine-calcium values in patients with an anatomical abnormality of the kidneys, a history of recumbency, or a family history of stone, does not differ significantly from that of stone patients in general. In patients with histological evidence of chronic pyelonephritis, the incidence of high urine-calcium values is approximately the same as that in healthy adults.

No evidence of sarcoidosis, multiple myeloma, hypervitaminosis D, or milk-drinker's syndrome was found in this series. Three patients had

hyperchloræmic acidosis with nephrocalcinosis, but only 1 of these patients exhibited in full the generally accepted picture of renal acidosis. In the 2 remaining patients there was considerable impairment of glomerular function, and the urinary excretion of calcium was lower than normal.

Parathyroid adenoma or hypertrophy was found at neck exploration in 2·3 per cent of the stone patients in our series, but this may not represent the total incidence since Albright and Reifenstein (1955) and Keating (1955) have reported an incidence of approximately 5 per cent in two widely separated areas in the U.S.A. In many cases the diagnosis of primary hyperparathyroidism depends almost entirely on the chemical findings, in particular on the presence of high serum- and urine-calcium levels. The normal range of serum-calcium is often stated to be 9·0–11·0 mg. per cent, but Keating (1955) reported that at the Mayo Clinic at least one in every five patients with primary hyperparathyroidism had average serum-calcium values within the range 10·5–11·0 mg. per cent, and it is of interest, therefore, to consider the average serum-calcium values of the patients in our series. The distribution of values in our series is shown in *Table IV*.

Table IV.—THE DISTRIBUTION OF SERUM-CALCIUM VALUES IN 344 PATIENTS WITH CALCIUM STONE OF RENAL ORIGIN

Average Serum-calcium (mg. per cent)	*Number of Patients*
7·6 to 8·0	2
8·1 to 8·5	4
8·6 to 9·0	7
9·1 to 9·5	31
9·6 to 10·0	101
10·1 to 10·5	114
10·6 to 11·0	64
11·1 to 11·5	12
11·6 or higher	9
Total	344

Eighty-five patients (58 men and 27 women) had average serum-calcium values of 10·6 mg. per cent or higher, but only 31 of these patients (21 men and 10 women) had urine-calcium values in excess of 300 mg. per day for men and 250 mg. per day for women. The remainder had normal or low urine-calcium values, 4 men and 2 women having evidence of poor renal function.

The 8 patients in our series (6 women and 2 men) in whom primary hyperparathyroidism was established by neck exploration had average serum-calcium values of 11·2 mg. per cent or higher. All except one of these patients had high urine-calcium values, the one exception being a woman with impaired renal function (urea clearance 40 per cent of normal). Patients with average serum-calcium values greater than 10·5 mg. per cent who also have high urine-calcium values or poor renal function are being kept under observation with a view to subsequent neck exploration.

In our experience the serum-phosphate level has proved to be of limited diagnostic value owing to the wide variation. Low values (2·0–2·5 mg. per cent) were commonly found accompanying hypercalciuria with or without hypercalcæmia (Albright, Hennemen, Benedict, and Forbes, 1953), but normal values (3·0–4·5 mg. per cent) were also found and these could not be accounted for by impaired renal function.

The Excretion of Inorganic Phosphate by Normal Individuals and Stone Patients on Normal Diet.—The daily excretion of inorganic phosphate by healthy adults is about 800 mg., but there is a considerable variation above and below this value. The urinary excretion of inorganic phosphate is influenced by the dietary intake of phosphorus, but dietary variations account for only a part of the difference in excretion of inorganic phosphate between normal individuals. The effect of variations in dietary intake of phosphorus on the urinary excretion of inorganic phosphate was determined by calculating the regression line of phosphate excretion upon dietary intake using the data available for 130 normal adults. This was obtained by reference to the following literature: Blatherwick and Long (1922); Hart, Tourtellotte, and Heyl (1928); Leverton and Marsh (1942); McClellan and others (1930); Pittman and Kunerth (1939); Tibbets and Aub (1937); Sherman (1920); Sherman, Gillet, and Pope (1918 a); Sherman, Wheeler, and Yates (1918 b); Sherman and Winters (1918).

The equation for the regression line was found to be:—

$$y = 365 + 0{\cdot}23\,x$$

where x = Intake of phosphorus in the diet (mg. per 24 hr.) and
y = Urinary excretion of inorganic phosphate (mg. P per 24 hr.)

We estimate that the intake of phosphorus on our normal ward diet is within the range 1100 ± 300 mg. per 24 hr., which corresponds to a variation in the urinary excretion of inorganic phosphate of ± 11 per cent. The phosphorus content of normal adult diets does not, in general, greatly exceed the range of 1100 ± 400 mg. per 24 hr., and this corresponds to a variation of ± 15 per cent in the urinary excretion of inorganic phosphate.

The distribution of urine-phosphate values for 92 normal men and 118 normal women on phosphorus intakes within the range 1100 ± 400 mg. per day are shown in *Fig.* 20, the data being obtained by reference to the following literature: Blatherwick and Long (1922); Hart and others (1928); Hyde (1940); McClellen and others (1930); Pittman and Kunerth (1939); Rich (1927–8); Sherman (1920); Sherman and others (1918 a, 1918 b); Sherman and Winters (1918); Tibbets and Aub (1937).

The distribution of urine-phosphate values for the normal men differs significantly from the distribution for normal women and it is important therefore that comparisons between normal adults and stone patients should be made between groups of the same sex. In *Fig.* 21 A the distribution of urine-phosphate values for normal men is given together with the distribution for 198 male stone patients from our series. The distributions for normal women and 108 female stone patients from our series are given in *Fig.* 21 B.

No significant difference could be found between the distribution for normal men and male stone patients, but a small group of female stone patients appear to have abnormally high values. Thus, 17 female stone patients, or 15·7 per cent of the total female stone patients, had urine-phosphate values greater than 900 mg. per day compared with 3·4 per

cent of the normal women. In 11 of these 17 patients the high phosphate excretion was associated with a high calcium excretion, and 4 of these 11 cases had high or moderately high serum-calcium values (10·5 mg. per cent or higher). One of these 4 patients had

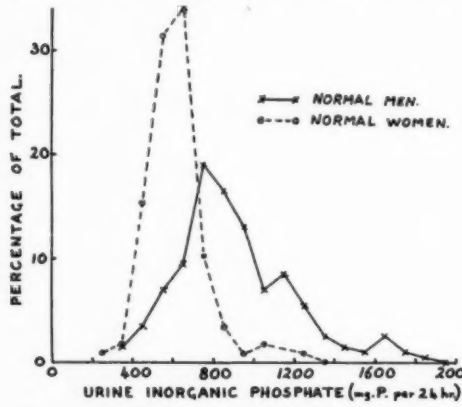
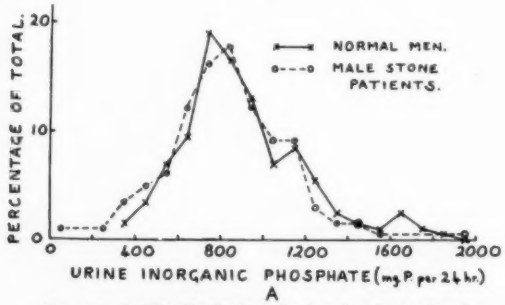


FIG. 20.—The distribution of urine-phosphate values for 92 normal men and 118 normal women on normal diet.

an average serum-calcium of 11·2 mg. per cent and was found to have a parathyroid adenoma. The other 3 patients had average serum-calcium values



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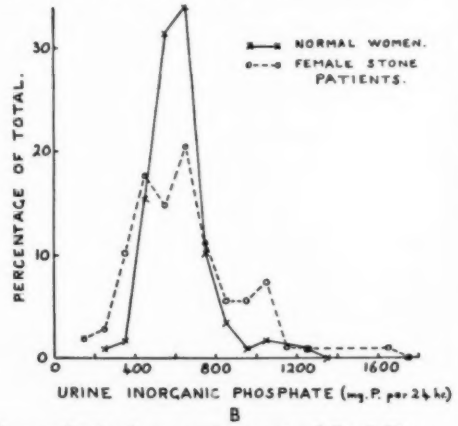

B

FIG. 21.—A, The distribution of urine-phosphate values for normal men and 198 male stone patients on normal diet. B, The distribution of urine-phosphate values for normal women and 108 female stone patients on normal diet.

of 10·5, 10·6, and 10·9 mg. per cent, and are regarded at present as possible cases of primary hyperparathyroidism. Three of the 17 patients had low urine-calcium values (49 to 112 mg. per day), associated with poor renal function and normal to low serum-calcium values (10·5 mg. per cent or lower).

Urine-phosphate values greater than 1000 mg. per day are generally associated with urine-calcium values of 300 mg. per day or higher in both male and female stone patients. Similarly, high calcium excretion is generally associated with high phosphate excretion, but these relationships do not always hold true, as is shown by the following examples of stone patients on normal diet taken from our series (*Table V*).

The incidence of high urine inorganic phosphate values in normal individuals and in patients with different types of stones is shown in *Table VI*. For the purpose of comparison, a urinary excretion of inorganic phosphate of 900 mg. P per day is taken as an arbitrary base line.

There appears to be no significant difference in phosphate excretion between normal men and male

Table V.

PATIENT	SEX	URINE-CALCIUM (mg. per 24 hr.)	URINE INORGANIC PHOSPHATE (mg. P per 24 hr.)	RENAL FUNCTION
E. J.	F.	49	1014	Poor
C. G.	M.	146	1140	Good
S. N.	F.	51	494	Poor
N. L.	F.	410	640	Good
F. B.	M.	480	591	Good
J. B.	M.	436	1280	Good

stone patients. Some differences may occur between normal women and women with stones of different types, but the samples available at present are too small to define any such differences with accuracy.

DISCUSSION

In considering the importance of high calcium excretion as a factor in the formation of calcium stones of renal origin, the following points appear to be relevant :—

1. The incidence of high urine-calcium values is appreciably greater in stone patients than in normal individuals (*see Table I*).

2. There is a higher incidence of stone and of high urine-calcium values in men than in women (*see Table I*).

3. There appears to be a definite relationship between the incidence of high urine-calcium values and the structure and chemical composition of stones (*see Table II*).

4. A high urinary excretion of calcium is a constant finding in renal acidosis, multiple myeloma, and primary hyperparathyroidism, and the incidence of stone is higher in these patients than in the population as a whole (Boyce, Garvey, and Northfleet, 1955).

These observations suggest that a high urinary excretion of calcium is an important factor in stone formation, but the following facts must also be considered.

1. A high urinary excretion of calcium is not found in all stone patients. Approximately two-thirds of the patients in our series had average urine-calcium values within or below the normal ranges (100–300 mg. per day for men, 100–250 mg. per day for women). Some of the 'normal' or low values are probably due to poor renal function, but this does not account for all the normal or low calcium values (*see Table I*).

2. High urinary excretion of calcium is not restricted to patients with calcium stone. Approximately 8 per cent of normal adults were found to have urine-calcium values greater than 300 mg. per day for men and 250 mg. per day for women, whereas the incidence of calcium stone of renal origin in the general population is probably less than 0·2 per cent (0·38 per cent of patients admitted to Leeds General Infirmary and St. James's Hospital, Leeds, in 1953–54 were found to have renal stone—Pyrah and Raper, 1955). Moreover, not all patients with renal acidosis, multiple myeloma, or primary hyperparathyroidism have urinary calculi, although a high urinary excretion of calcium is a constant finding in these patients.

It could be argued that although a high calcium excretion is not seen in all stone patients presenting at the clinic, it may have occurred at some time previously, or it might occur intermittently and could therefore be overlooked. Our records over the last few years, and the long-term studies by Nicolaysen and others (1953) on normal individuals, and by Cottet and Vittu (1955) on stone patients, do not support this view. In healthy adults and in the majority of stone patients the daily excretion of calcium appears to remain relatively constant over long periods providing there is no marked change in calcium intake in the diet. A few exceptions are known, but these apply to only a small proportion of stone patients. For example, the urinary excretion of calcium is raised during periods of immobilization (Deitrick and others, 1948; Cordonier and Talbot, 1948), and in progressive diseases such as primary hyperparathyroidism. Our observations on the relationship between renal function and calcium excretion suggest that the latter will decrease progressively in chronic renal diseases and it is of interest to note that renal stone is not generally found in patients with chronic nephritis.

Hyperphosphaturia does not appear to be an important factor in the formation of calcium stones, but it would be expected that a high phosphate excretion would increase the tendency for stones to form. From preliminary studies in this laboratory it would appear that hypercalciuria is generally accompanied by a higher than average excretion of inorganic phosphate and also an increased excretion of oxalic acid. It seems probable therefore that crystallization plays an important part in stone formation in patients with hypercalciuria, and this view is supported by the apparent existence of a relationship between calcium excretion and the structure of the stone.

Table VI.—The Relationship between the Urinary Excretion of Inorganic Phosphate and the Type of Stone

Group	Men		Women	
	Number of Individuals	Urine Inorganic Phosphate (Percentage with values greater than 900 mg. P per day)	Number of Individuals	Urine Inorganic Phosphate (Percentage with values greater than 900 mg. P per day)
Normal individuals	200	43	118	3·4
Calcium-phosphate stone	4	25	8	12
Calcium-oxalate stone	37	43	8	25
Mixed calcium-oxalate—calcium-phosphate stone	12	36	16	19
Mixed struvite—calcium-phosphate stone	7	Nil	7	Nil

Prien (1955) has reviewed some of the relationships between the composition of urinary calculi and the clinical case history. Calcium stones of renal origin vary widely in composition and structure and several different structures may occur in a single stone. Much remains to be done with regard to correlating the fine structure of stones with the clinical history and biochemical status of the patient.

SUMMARY

1. A detailed survey has been made of the urinary excretion of calcium and inorganic phosphate by normal adults and patients with calcium stone of renal origin.

2. The effect of normal variations in the intake of calcium and phosphorus on the urinary excretion of calcium and inorganic phosphate is small compared with the effect of physiological variations between individuals. It is permissible therefore to compare the distribution of urine-calcium and inorganic phosphate values for normal adults with the distribution for a group of adult stone patients.

3. The normal range for the urinary excretion of calcium by adults on normal diet is approximately 100–300 mg. per day for men and 100–250 mg. per day for women. The corresponding ranges for the urinary excretion of inorganic phosphate are 500–1500 mg. per day for men and 500–900 mg. per day for women.

4. The urinary excretion of inorganic phosphate by stone patients does not differ appreciably from that of normal individuals.

5. The urinary excretion of calcium is depressed if there is appreciable impairment of renal function, and it was found that approximately 11 per cent of the patients in this present series had evidence of poor renal function. After omitting these patients it was found that 59 per cent of the remainder had average urine-calcium values greater than 200 mg. per day, compared with 26 per cent of normal adults.

6. The incidence of high urine-calcium values is greater in normal men than in normal women.

7. In stone patients the incidence of stone and of high urine-calcium values is greater in men than in women.

8. The incidence of high urine-calcium values in patients with a history of recumbency at some time in the past, a family history of stone, or an anatomical abnormality of the kidneys, was approximately the same as that in stone patients as a whole.

9. Parathyroid adenoma or hypertrophy was found at neck exploration in 2·3 per cent of the patients in this series. The problem of diagnosing primary hyperparathyroidism is discussed, and the average serum-calcium values of the 344 patients in this series are reviewed.

10. The urinary excretion of calcium in relation to the chemical composition and structure of stone is considered, and it is concluded that a high urinary excretion of calcium does not, by itself, result in stone formation, but it increases the chance that stone formation will occur, and it appears to influence the type of stone formed.

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REFERENCES

ALBRIGHT, F., HENNEMAN, P., BENEDICT, P. H., and FORBES, A. P. (1953), *Proc. R. Soc. Med.*, **46**, 1077.
— — and REIFENSTEIN, E. C. (1948. *The Parathyroid Glands and Metabolic Bone Disease: Selected Studies*. Baltimore: Williams and Wilkins.
— — — — (1955), quoted in *Brit. med. J.*, **2**, 1314.
BLATHERWICK, N. R., and LONG, M. L. (1922), *J. biol. Chem.*, **52**, 125.
BOGERT, L. J., and MCKITTRICK, E. J. (1922a), *Ibid.*, **54**, 363.
— — — — (1922b), *Ibid.*, **54**, 375.
BOYCE, W. H., GARVEY, F. K., and NORFLEET, C. M. (1955), *Amer. J. Med.*, **19**, 87.
BREITER, H., MILLS, R., DWIGHT, J., MCKEY, B., ARMSTRONG, W., and OUTHOUSE, J. (1941), *J. Nutr.*, **21**, 351.
BRICKER, M. L., SMITH, J. M., HAMILTON, T. S., and MITCHELL, H. H. (1949), *Ibid.*, **39**, 445.
CORDONIER, J. J., and TALBOT, B. S. (1948), *J. Urol.*, **60**, 316.
COTTET, J., and VITTU, C. (1955), *Pr. méd.*, **63**, 878.
DEITRICK, J. E., WHEDON, G. D., and SHORR, E. (1948), *Amer. J. Med.*, **4**, 3.
FLOCKS, K. H. (1939), *J. Amer. med. Ass.*, **113**, 1466.
HART, M. C., TOURTELLOTTE, D., and HEYL, F. W. (1928), *J. biol. Chem.*, **76**, 143.
HEGSTED, D. M., MOSCOSO, I., and COLLAZOS, C. (1952), *J. Nutr.*, **46**, 181.
HUNSCHER, H. A., DONELSON, E., ERICKSON, B. N., and MACY, J. G. (1934), *Ibid.*, **8**, 341.
HYDE, E. (1940), *J. biol. Chem.*, **134**, 95.
KEATING, F. R. (1955), Post Graduate Seminar: N. Central Sect. Amer. med. Ass.
KNAPP, E. L. (1947), *J. clin. Invest.*, **26**, 182.
LEVERTON, R. M., and MARSH, A. G. (1942), Nebraska Exptl. Station Research Bull., No. 125.
MCCANCE, R. A., and WIDDOWSON, E. M. (1939), *Biochem. J.*, **33**, 523.
— — — — (1942), *J. Physiol.*, **101**, 44.
— — — — and LEHMANN, H. (1942), *Biochem. J.*, **36**, 686.
MCCLELLAN, W. S., RUPP, V. R., and TOSCANI, V. (1930), *J. biol. Chem.*, **87**, 669.
MCGEOWN, M. G., and BULL, G. M. (1957), *Brit. med. Bull.*, **13**, 53.
MALM, O. J. (1953), *Scand. J. clin. lab. Invest.*, **5**, 75.
NICOLAYSEN, R., EEG-LARSEN, N., and MALM, O. J. (1953), *Physiol. Rev.*, **33**, 424.
OWEN, E. C., IRVING, J. J., and LYALL, A. (1940), *Acta med. scand.*, **103**, 235.
PITTMAN, M. S., and KUNERTH, B. L. (1939), *J. Nutr.*, **17**, 175.
PRIEN, F. L. (1955), *J. Urol.*, **73**, 627.
PYRAH, L. N., and RAPER, F. P. (1955), *Brit. J. Urol.*, **27**, 333.
RICH, G. R. (1927–28), *Proc. Soc. exp. Biol., N.Y.*, **25**, 307.
SHERMAN, H. C. (1920), *J. biol. Chem.*, **41**, 173.
— — GILLET, L. H., and POPE, H. M. (1918a), *Ibid.*, **34**, 373.
— — WHEELER, L., and YATES, A. B. (1918b), *Ibid.*, **34**, 383.
— — and WINTERS, J. C. (1918), *Ibid.*, **35**, 309.
STEGGERDA, F. R., and MITCHELL, H. H. (1939), *J. Nutr.*, **17**, 235.
— — — — (1941), *Ibid.*, **21**, 577.
— — — — (1946), *Ibid.*, **31**, 423.
— — — — (1951), *Ibid.*, **45**, 201.
STRIEBEL, A., and VIOLLIER, G. (1949), *Helvet. med. Acta*, **16**, 428.
SUTHERLAND, J. W. (1954), *Brit. J. Urol.*, **26**, 22.
TIBBETS, D. M., and AUB, J. C. (1937), *J. clin. Invest.*, **16**, 491.

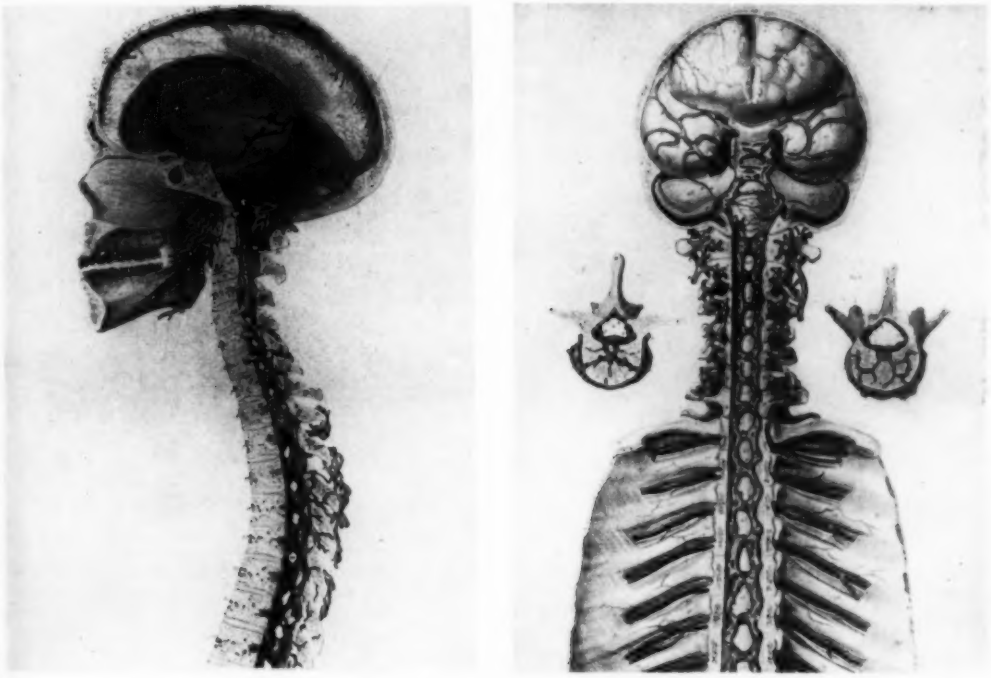
OSTEOMYELITIS AS A COMPLICATION IN UROLOGY

WITH SPECIAL REFERENCE TO THE PARAVERTEBRAL VENOUS PLEXUS

By C. Q. HENRIQUES, London

"Metastatic abscesses and metastatic tumours can appear in locations that do not seem to be in line of direct spread from their primary focus. There is even a regularity of distribution of these paradoxic metastases."—Batson (1940)

The urinary tract has been put forward from time to time as a possible source of infection in osteomyelitis, but its special relationship to lesions of the spine has not been fully appreciated. Furthermore, whilst localized inflammation of the pubic bones is a recognized complication of prostatic surgery, its occasional spread to involve the acetabula with serious consequences to one or both hip-joints, as pointed out by Silver (1941), has received little comment.



A B

Fig. 22.—The paravertebral venous plexus, showing its connexions with the segmental veins, cranial venous sinuses, and the vertebral bodies. (Reproduced from Berschet's anatomical treatise, first published in 1832.)

To explain the special association between infections of the urinary tract and osteomyelitis of the spine, hips, and pelvis, it is necessary to demonstrate an anatomical pathway linking it with these bones.

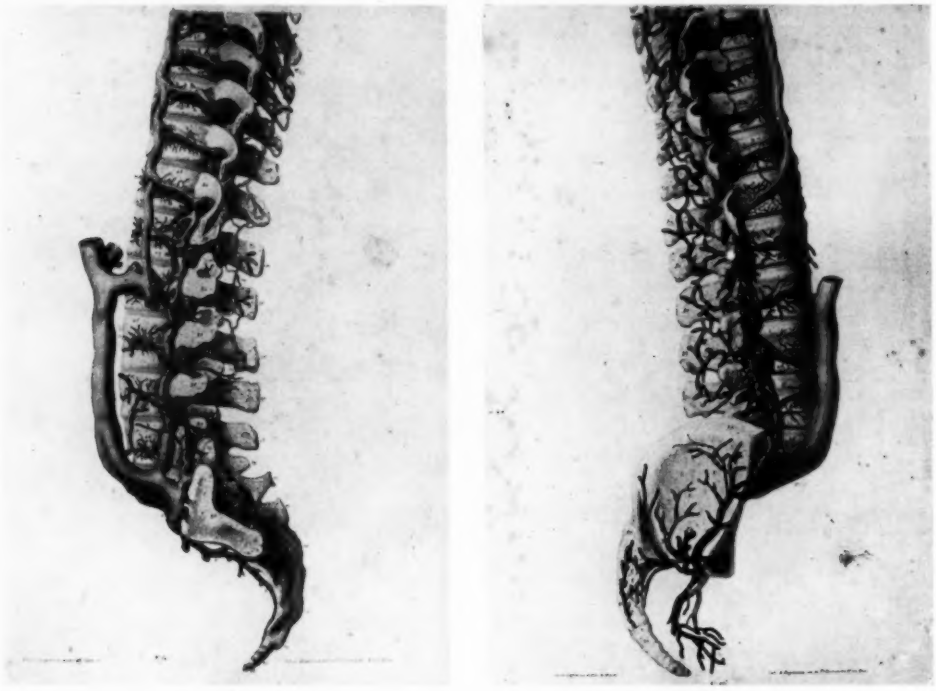
ANATOMY

The complex venous network that invests the vertebral column, communicating with the pelvic venous plexus at one end and the intracranial venous sinuses at the other, was first described by Chaussier (1746–1828). Dupuytren also made it a subject of study and demonstrated the plexus in his lectures on anatomy (Quain, 1837), but it is the French surgeon and anatomist Gilbert Breschet (1832) who deserves most credit for the original anatomical studies. He injected the veins in question with a solution of isinglass and prussian blue and from the dissected specimens produced a beautifully illustrated treatise on the subject.

The connexions of this paravertebral venous plexus with the systemic veins, pelvic, lumbar intercostal, and vertebral, are clearly demonstrated (*Figs.* 22, 23) as are those with the intracranial venous sinuses. Particular attention is called to the rich anastomoses that this plexus forms with the venous channels within the vertebral bodies (*Figs.* 22, 24).

The physiology of this venous system was also discussed by these early writers. The thin walls of

the vessels and their complicated apparently purposeless meanderings suggested a sluggish flow of blood at low pressure. Quain comments on this and also on the connexions with the segmental systemic veins: "Each portion of the vertebral venous chain is, as it were, a separate trunk by itself, receiving blood and conveying it outwards to the general circulation, sluggish and the pressure low, and into which blood is forced during a rise in intra-abdominal or intra-thoracic pressure, as in coughing or straining. He suggests that the characteristic distribution of osseous metastases from carcinoma of the prostate is explained by the existence of this venous pathway, and points out that septic foci in the pelvis might be



A B

FIG. 23.—Showing the relation of the paravertebral veins to the lumbar and lower dorsal vertebræ and their systemic anastomoses. (Reproduced from Breschet's anatomical treatise, first published in 1832.)

for the current does not ascend or descend along the column which the series of veins forms." He further suggests that "the chief propelling power seems to be the physico-mechanical influence exerted by the thorax".

Batson (1940) using a mixture of radio-opaque water colour and thorium dioxide injected this venous system via the deep dorsal vein of the penis. Providing that the intra-abdominal pressure was raised he was able to fill the system in its entirety. From the prostatic plexus a multitude of venules ramify throughout the pelvic basin and pass to its outer aspect supplying the hip-joints in the process. The rich anastomoses formed between the vessels on the inner and outer aspects of the pelvis and their relation to the hip-joint were commented on by Ribet (1926). After filling the pelvic venules the dye spread throughout the paravertebral veins filling the segmental and shoulder-girdle vessels and finally entering the intracranial venous sinuses.

Batson postulates that this venous system forms a series of vast storage lakes in which the flow is expected to give rise to similarly sited septic emboli. Whilst the former concept is now widely accepted, the latter has, until recently, received scant attention.

These septic emboli give rise to a variety of bone lesions from the now well recognized, though aetiologically disputed, osteitis pubis to the rarer conditions of septic arthritis of the hip, and osteomyelitis of one or more vertebral bodies.

PATHOGENESIS

The earlier studies on osteomyelitis of the spine were, appropriately enough in view of the anatomical work mentioned, undertaken in France. The list of French authors is a long one, starting with Lannelongue's description of a case of osteomyelitis of a lumbar vertebra in 1897. Labyerie (1905) commented on the frequency with which the lumbar spine was involved as distinct from the dorsal and cervical vertebræ. The possibility of the urinary tract acting as a source of infection in these cases is frequently mentioned but seldom with conviction. Carson (1931) in presenting 4 cases of vertebral

Table I.—PUBLISHED CASES OF OSTEOMYELITIS WITH URINARY TRACT INFECTION

AUTHOR AND YEAR	AGE AND SEX	URINARY TRACT PATHOLOGY	OPERATION	SITE OF BONE LESION	WHEN HEALED (mth.)	ORGANISM	CULTURES		
							Bone	Blood	Urine
Pedersen 1922	58 M.	Prostatitis	Prostatic massage	L. humerus		*Staphylococcus*			
Carson 1931	— M.	Prostatic abscess	Drainage	L.2, 3					
Selig 1934	37 M.	Nephrolithiasis	Cystoscopy	C.5, 6	5	*B. proteus*		+	
Kretschmer and Ockuly 1935	63 M.	Cystitis and retention	Cystostomy	L. tibia		*Staph. aureus*	+	—	+
	49 M.	Nephrolithiasis	Pyelolithotomy	D.6, 7	6	*B. proteus*			+
	67 M.	Cystitis and retention	Transvesical prostatectomy	R. hip-joint	4				
Flemming 1935	55 M.	Pyelonephritis	Nephrectomy	C.3, 4	3				
Wilson 1935	43 M.	Urinary infection	None	C.1, 3	4				
Kulowski 1936	— —	Prostatic abscess		Spine					
Stotz 1938	14 F.	Perinephric abscess		L.1					
Kusunoki 1938	— M.	Urethral stricture	Dilatation	D.9, 10, 11, 12		*Ps. pyocyaneus*			+
Schein 1940	56 M.	Nephrolithiasis	Cystoscopy	D.7, 8	4	*Ps. pyocyaneus*		+	+
Deming and Zaff 1943	66 M.	Benign prostatic enlargement	Transvesical prostatectomy	D.8, 9		*Esch. coli*		+	
	65 M.	Benign prostatic enlargement	Transurethral prostatectomy	L.1, 2	9				
	71 M.	Benign prostatic enlargement	Transvesical prostatectomy	L.4, 5		*Str. hæmolyticus*		+	
Donahue 1949	71 M.	Benign prostatic enlargement	Transvesical prostatectomy	D.10, 11					
	60 M.	Urethral stricture	Dilatation	L.2, 3		*Esch. coli*			+
Hurwitz and Albertson 1950	55 M.	Chronic retention—median bar	None	C.4, 5, 6	15	*Esch. coli*	+	—	+
Alderman and Duff 1952	66 M.	Benign prostatic enlargement	Cystostomy	C.4, 5	4	*B. proteus*		+	+
Chrichton and Hamman 1953	59 M.	Benign prostatic enlargement	Transvesical prostatectomy	D.7, 8, 9		*Sal. typhosa*		+	
Wood 1954	65 M.	Bladder neoplasm	Partial cystectomy	R. hip-joint		*Staph. aureus*	+		
	54 M.	Benign prostatic enlargement	Transvesical prostatectomy	L. hip-joint	15	*Esch. coli*			+
	— M.	Benign prostatic enlargement	Retropubic prostatectomy	L. spine					
	— M.	Urethral stricture	Dilatation	L. 2					
Mussey 1954	55 M.	Bladder neck obstruction	Catheterization	L.2, 3; R. sacro-iliac joint	10	*Esch. coli*		—	+
	61 M.	Urethral stricture	Dilatation	L.4, 5				—	
De Feo 1954	70 M.	Benign prostatic enlargement	Transvesical prostatectomy	L.2, 3	2				
	59 M.	Benign prostatic enlargement	Transvesical prostatectomy	D.6, 7	2				
Leigh, Kelly, and Weens 1955	74 M.	Benign prostatic enlargement	Cystostomy	L.5; S.1					
	63 M.	Nephrolithiasis	Pyelolithotomy	D.7, 8; L.1, 2		*Ps. pyocyaneus*	+		
	53 M.	Urethral stricture	None	D.7,8		*P. vulgaris*	+		
	54 F.	Urinary infection	Cystoscopy	L.2, 3					
	58 F.	Urinary infection	None	D.7, 8		*Esch. coli*	+		
	49 M.	Nephrolithiasis	None	D. spine			—		
	53 F.	Nephrolithiasis	Pyelolithotomy	L.1, 2, 3					
	57 M.	Urethral stricture	Dilatation	L.3, 4		*Staph. aureus*	+		
	60 M.	Urinary infection	None	L.3, 4		*B. proteus*			+
Henson and Coventry 1956	79 F.	Urinary infection	None	D.8, 9, 10	8	*Esch. coli*		+	+
	69 F.	Nephrolithiasis	None	D.4, 5	9	*Esch. coli*			+
	40 F.	Urinary infection	None	L.4	3	*M. pyogenes*	+		
	42 M.	Urethral stricture	Dilatation	L.2; L. sterno-clavicular joint	2	*M. pyogenes*	+		+
	70 M.	Nephrolithiasis	Ureterolithotomy	L.3, 4	5	*A. fæcalis*	+		
	51 M.	Urethral stricture	None	L.4, 5	3	*Esch. coli*	+		+
	50 M.	Nephrolithiasis	Cystoscopy	D.11, 12; L.1, 2	6	*Pseudomonas*	+		
Lame 1956	61 M.	Benign prostatic enlargement	Transurethral prostatectomy	L.1, 2	6			—	
	55 F.	Carcinoma of rectum	Abdomino-perineal	L.1, 2, 3, 4					
	65 M.	Adenoma of sigmoid colon	Sigmoid polypectomy	D.7, 8	3			—	
Liming and Youngs 1956	87 M.	Benign prostatic enlargement	Transurethral prostatectomy	L.2, 3	7	*B. aerogenes, Ps. pyocyaneus*			+
	71 M.	Prostatitis	Transurethral prostatectomy	D.4, 5		*B. aerogenes*		+	+
Henriques 1958	43 M.	Urethral stricture	Dilatation and cystostomy	L.3, 4	10	*Esch. coli*		—	+
	74 M.	Benign prostatic enlargement	Retropubic prostatectomy	C.2, 3, 4; D.9, 10		*Staph. aureus*	+		
	75 M.	Bladder neck obstruction	Transurethral resection	L.4, 5; L. hip	7; 13	*P. vulgaris, Ps. pyocyaneus*			+
	73 M.	Benign prostatic enlargement	Cystostomy	R. shoulder joint	4	*Esch. coli, staphylococcus*	—		+
	65 M.	Benign prostatic enlargement	Retropubic prostatectomy	R. hip joint	9	*Staph. aureus*	+		
	53 M.	Urinary infection	None	L.2, 3	9	*Str. hæmolyticus*	—		+

osteomyelitis, all of which had infected urine and one a prostatic abscess, none the less ascribes the primary focus to a boil in 3 cases and to a subcutaneous abscess in the fourth. He does, however, make the still important point that ever since the true nature of Pott's disease was recognized by the French in

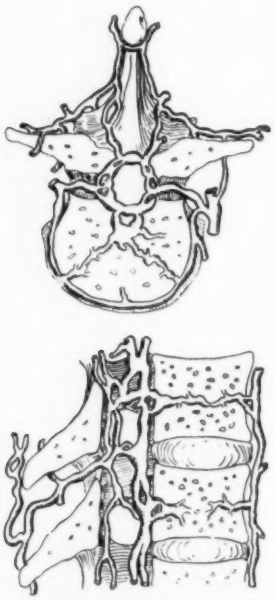


FIG. 24.—Diagram of transverse and sagittal sections of the vertebral column to show the main connexions made by the paravertebral veins with the substance of the vertebral bodies (*see* inset *Fig.* 22B).

1825, tuberculosis has come to overshadow all other inflammatory lesions in the spine, and many cases of non-proven senile tubercle may have been, and still may be, due to other organisms. When considering the possibility that the source of the infection may lie in the lower urinary tract it is perhaps significant that a constant predilection is shown for the lumbar spine (54·6 per cent), followed by the dorsal spine (25·9 per cent), the least common site being the cervical spine (10·3 per cent). Henson and Coventry (1956), from whom these figures are quoted, point out that this distribution accords well with the conception of showers of organisms being released into the paravertebral venous network from a focus in the lower urinary tract.

Table I shows in summarized form the cases hitherto published in which there is a definite association between urinary tract infection and osteomyelitis. Of the 55 cases, all but 11 followed operation. The distribution of the vertebral lesions, lumbar 27, dorsal 17, and cervical 6, parallels the figures given above, and in addition to the spine, the hip-joint was affected in 5 cases, the shoulder-joint in 2 cases, the sterno-clavicular joint in 1 case, the sacro-iliac joint in 1 case, and the tibia in 1 case.

The causative organisms were isolated by direct culture from the bone or joint in 13 cases and the blood-culture was positive in 8 out of 15 cases. *Table II* shows the organisms obtained from these two sources and also the organisms found in the urine. The common offenders are *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas pyocyaneus*, and *Proteus vulgaris*.

Details of 40 operations are given in the literature and no less than 33 of these were performed on the urethra, prostate, or bladder. It is interesting to note

Table II.—NUMBER OF CASES IN WHICH CAUSATIVE ORGANISMS WERE ISOLATED

ORGANISM	BONE	BLOOD	URINE
Staph. aureus	5	—	2
Esch. coli	3	2	9
Ps. pyocyaneus	2	1	4
P. vulgaris	1	2	4
M. pyogenes	2	—	1
B. aerogenes	—	1	2
Str. hæmolyticus	—	1	1
A. faecalis	1	—	—
Sal. typhi	—	1	—

that 2 cases of vertebral osteomyelitis followed operations on the sigmoid colon and rectum respectively, the latter having a definite urinary infection post-operatively (Lame, 1956). The nature of the various operations is analysed in *Table III*.

Table III.—OPERATIONS PERFORMED

Operations on Prostate—17 Cases	
Transvesical prostatectomy	7
Transurethral prostatectomy	5
Retropubic prostatectomy	3
Drainage of prostatic abscess	1
Prostatic massage	1
Urethral Instrumentation—12 Cases	
Dilatation of stricture	7
Cystoscopy	4
Catheterization	1
Operations on Bladder—4 Cases	
Suprapubic cystostomy	3
Partial cystectomy	1
Operations on Kidney and Ureter—4 Cases	
Nephro- and pyelolithotomy	3
Ureterolithotomy	1
Nephrectomy	1
Operations on other Pelvic Viscera—2 Cases	
Abdomino-perineal resection of rectum with hysterectomy	1
Sigmoid polypectomy	1

In the following six cases of osteomyelitis described, five followed operations on the lower urinary tract, and one occurred spontaneously in the presence of urinary infection.

CASE REPORTS

Case 1.—Male, aged 43 years. Gonorrhœa in 1953 resulting in urethral stricture. Suprapubic cystostomy March 14, 1956 after attempted dilatation of stricture. Successful dilatation April 5, which was followed by rigors and fever for several days. Eight weeks later he developed pain in the lumbar region radiating to the right groin which became increasingly severe. The urine contained many pus cells and culture grew *Esch. coli* and enterococci in profusion. He had pyrexia up to 100° F., the white-cell count was 8600 per c.mm., the E.S.R. 10 mm. per hour (Westergren), and the blood-culture was sterile. A diagnosis of acute pyelitis was made, but the condition failed to respond to antibiotic therapy and his pain worsened. The urinary organisms varied in

subsequent specimens from coagulase-negative staphylococci to *P. vulgaris* and *Ps. pyocyaneus*.

On Sept. 17 (twenty-three weeks after the urethral dilatation) rarefaction of the lower border of the third lumbar vertebra near its anterior margin was visible on radiography; by Sept. 24 the lesion was seen to involve the upper border of the fourth lumbar vertebra as well (*Fig.* 25).

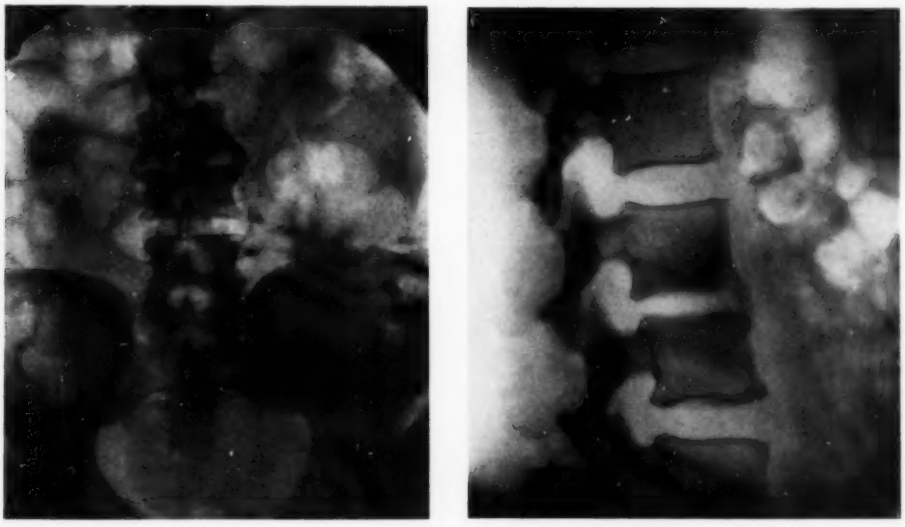
The spine was immobilized in a plaster jacket and the urinary infection treated. Healing was evident two months later and was complete by March 3, 1957, ten months from the onset of symptoms (*Fig.* 26).

Case 2.—Male, aged 74 years. Retropubic prostatectomy for benign prostatic enlargement Feb. 22, 1957. Urine sterile before operation. Severe secondary hæmorrhage and clot retention necessitating catheterization on the eighth day. Two days later he became febrile and the hæmoglobin had fallen to 56 per cent. The urine contained pus cells and culture grew *Esch. coli*, the white-cell count being 15,200 per c.mm. The fever lasted for fifteen days during which the patient was given terramycin.

He was discharged on March 18 but had to be readmitted on April 3 because of severe pain and limitation of movement of his neck, together with a developing paraplegia. He was again pyrexial, the hæmoglobin was down to 58 per cent, and the white-cell count 16,000 per c.mm. The urine contained pus cells and culture grew *P. vulgaris*. X-ray examination revealed two vertebral lesions, one involving the second, third, and fourth cervical vertebræ, the other the ninth and tenth dorsal vertebræ (*Fig.* 27), together with the intervening disks in all cases.

With immobilization of his neck in extension in plaster the paraplegia rapidly resolved, but the patient remained extremely ill and debilitated and he died on May 5. The affected portions of the spine were removed at autopsy and cultures from the involved vertebræ grew *Staph. aureus* and enterococci. The latter may have been post-mortem invaders, the staphylococci were almost certainly present in life. Longitudinal section of the vertebræ showed complete destruction of the disks with partial collapse and fragmentation of the vertebral bodies (*Fig.* 28). A slit-like cavity lined with bone spicules and a little granulation tissue, but containing no frank pus, was present at the site of the collapse.

FIG. 25.—*Case* 1. Osteomyelitis of the third and fourth lumbar vertebræ following dilatation of a urethral stricture; early stage of lesion.



A B

FIG. 26.—*Case* 1. Appearance six months later of the healed lesion with well marked bony bridging between the affected vertebræ.

The report on the histological features, for which I am indebted to Dr. M. E. A. Powell, is as follows: "Sections of the vertebral bodies bordering the area of collapse from both the cervical and dorsal regions show a similar histological picture. There is superficial destruction of the nature, but in some areas shows foci of acute inflammatory change, some of which surround fragments of dead bone and include occasional foreign-body type giant cells. The appearance is that of the healing stage of a non-specific osteomyelitis."

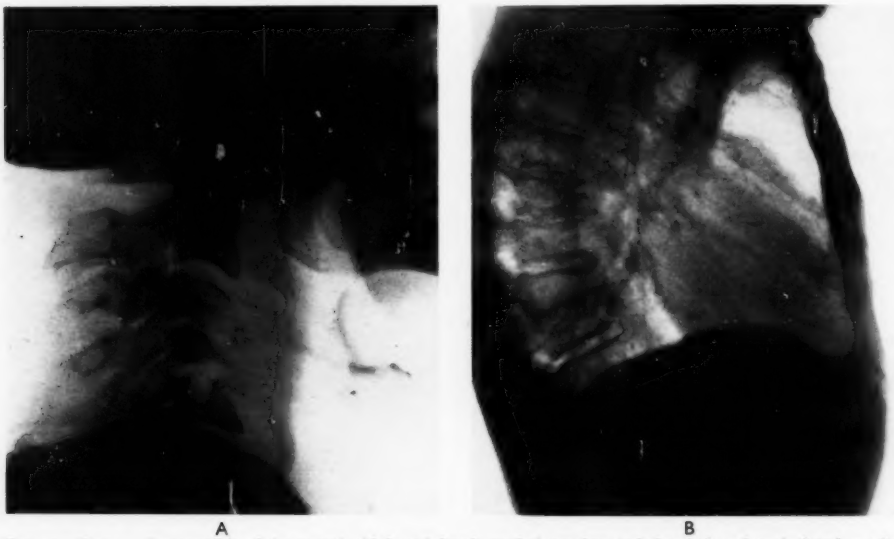


FIG. 27.—*Case* 2. Osteomyelitis of the second, third, and fourth cervical vertebræ and the ninth and tenth dorsal vertebræ following retropubic prostatectomy.

FIG. 28.—*Case* 2. Vertical sections through the dorsal and cervical spines showing the abscess cavities in each case. Note complete destruction of the disk involved and the relation of the spinal cord to the cervical lesion.

FIG. 29.—*Case* 3. Osteomyelitis of the lumbar spine following retropubic prostatectomy and associated with osteitis pubis.

bony trabeculæ adjacent to the cavities with replacement by a narrow zone of fibrotic granulation tissue. This granulation tissue is patchily infiltrated by an inflammatory exudate which is for the most part chronic in

Case 3.—Male, aged 75 years, a diabetic. Retropubic prostatectomy Nov. 4, 1953 for benign enlargement of the prostate. On the eleventh day after operation he had a severe secondary hæmorrhage necessitating blood transfusion.

The hæmaturia persisted for two weeks, during which time he received a total of 6 pints of blood. He developed a high fever which was controlled by terramycin, having failed to respond to aureomycin. Four weeks after operation a bed sore appeared in the sacral region and although this healed slowly, further pressure sores appeared over the trochanteric regions as a result of nursing the patient on his side.

In January, 1954, he developed a urinary fistula in the abdominal scar at the site of the retropubic stab-drain. This was associated with osteitis pubis which had led in this case, as so often, to gross bladder neck fibrosis and obstruction. At this time he was febrile, anæmic (hæmoglobin 64 per cent), his diabetes was unstabilized, and his urine heavily infected with *Esch. coli* and *P. vulgaris*. After bladder irrigation, antibiotic therapy, and blood transfusion, a transurethral resection of the bladder neck was performed on Feb. 2. The fever persisted and the urine remained infected with a variety of organisms, notably *Ps. pyocyaneus* and *P. vulgaris*.

Three weeks later the patient developed pain in the lumbar spine, and after a further eight weeks destruction of the anterior aspects of the 4th and 5th lumbar vertebræ with obliteration of the disk space was evident on radiography (*Fig.* 29).

FIG. 30.—*Case* 3. Osteitis pubis showing destruction of the symphysis. Note generalized rarefaction of pelvic bones.

FIG. 31.—*Case* 3. The pubic lesion has healed but arthritis of the left hip is developing.

FIG. 32.—*Case* 3. Complete destruction of the head of the left femur has occurred.

Three and a half months later this lesion had healed with new bone formation, but he still had severe osteitis pubis with widening of the symphysis, and rarefaction of the pubic rami was now evident (*Fig.* 30). This in turn healed readily, with much bony sclerosis and bridging, in just over two months (*Fig.* 31), but by now the patient had developed an acute arthritis of the left hip, and erosion of the femoral head was visible. By Oct. 3, 1955 the head of the left femur had been completely eroded, a shelf of new bone was forming above the acetabulum, and the whole pelvis was recalcifying (*Fig.* 32).

Traction was applied to the limb at the onset of symptoms and maintained for eight months, after which the patient was allowed to walk with elbow crutches. He was discharged on Oct. 30 walking well, with a pain-free

flexion range of 40° in the left hip. He was free from urinary infection.

This patient was quite exceptional in having the misfortune to develop three bone lesions consecutively, but this must have been in large measure due to his debilitated state consequent on chronic anæmia, unstabilized diabetes, and an obstinate urinary infection. Noteworthy features are that his urine remained infected with a variety of organisms throughout the period in which the bone lesions developed, that none of the lesions suppurated, that they healed relatively quickly with much sclerosis and new bone formation, and that the residual disability was not great. It is not uncommon for osteitis pubis to lead to such scarring and contracture of the bladder neck that subsequent transurethral resection is required, as in this instance.

Case 4.—Male, aged 73 years. Suprapubic cystostomy for chronic retention of urine due to benign enlargement of the prostate Aug. 22, 1944. At this time the patient was febrile and his urine contained pus cells, *Esch. coli*, and enterococci. The white-cell count was 18,800 per c.mm. and the hæmoglobin 60 per cent. He was treated with sulphapyridine and sulphathiazole. Six weeks after operation he developed severe pain in the right shoulder and extreme limitation of movement. A few cubic centimetres of sterile pus were aspirated from the joint on Oct. 10. The urinary infection with *Esch. coli* persisted and now in addition staphylococci were grown on culture. On Oct. 19 a further 5 c.c. of sterile pus were aspirated from the right shoulder-joint. The fever had subsided by Oct. 22 and recovery was uneventful, the final range of movement in the shoulder being limited, but the functional disability minimal.

Transurethral resection of the prostate was performed on March 27, 1945 and the sections showed benign hyperplasia.

(This case is referred to by Wood, 1954.)

Case 5.—Male, aged 65 years. Retropubic prostatectomy for benign prostatic enlargement in March, 1956. Following operation the urine, which had previously been sterile, grew *Esch. coli* and enterococci on culture. A month later the patient developed an acute arthritis of his right hip, and erosion of the femoral head and narrowing of the joint space were visible on radiography by April 16. Definite destruction of the femoral head was evident by July 20 and the patient was readmitted to hospital. At this time the urine was infected with a resistant strain of *Esch. coli*, the white-cell count was 10,000 per c.mm. and the E.S.R. 80 mm. per hour (Westergren). On Aug. 18 the hip-joint was aspirated and 15 c.c. of blood-stained fluid were removed; culture grew *Staph. aureus* (coagulase positive).

The joint was immobilized by skin traction and sound bony ankylosis was obtained by January, 1957.

Case 6.—Male, aged 53 years. Admitted to hospital April 23, 1957 with pain in the lumbar spine radiating to the right hip of four months' duration. Examination revealed extreme limitation of movement of the lumbar spine and tenderness over the lumbar spinous processes. There was a moderate pyrexia, the white-cell count was 6100 per c.mm. and the E.S.R. 65 mm. per hour (Westergren). The urine contained numerous pus cells and culture grew hæmolytic streptococci (Lancefield type B). The anti-staphylococcal alpha hæmolysin titre in the blood was raised to 2–4 units per c.c. (normal 0·5–1·5 units per c.c.). The gonococcal complement-fixation test was also weakly positive. The X-ray examination revealed destruction of the contiguous portions of the second and third lumbar vertebræ and the intervening disk (*Fig.* 33).

This patient gave no definite history of urinary symptoms apart from occasional scalding and frequency over the past few months. Intravenous pyelography did not show any abnormality to account for his urinary infection.

Needle biopsy of the involved vertebræ was performed but no pus could be obtained for culture.

Whilst in this case there are three possible organisms responsible, the hæmolytic streptococcus, staphylococcus, or the gonococcus, the source must surely have been the lower urinary tract whichever was responsible, and the route of spread similar to the other cases described. It is of interest that no operation or urethral instrumentation was performed in this case. The patient was symptom-free by July, and the bone lesion had healed uneventfully by January, 1958.

FIG. 33.—*Case* 6. Osteomeylitis of the second and third lumbar vertebræ due to urinary infection.

CLINICAL FEATURES

The patient frequently has an obstinate urinary infection of long standing and is in poor general health. Several cases have shown a marked degree of anæmia often caused by secondary hæmorrhage in the post-operative period.

The bacteræmia which results from the operation, or which may occur spontaneously, usually gives rise to a moderate degree of fever and sometimes rigors. This period of constitutional disturbance occurs within days of the operation and may be very severe or so mild as to pass unnoticed.

Some weeks later the developing bone lesion manifests itself by pain in the affected region. The pain is often extremely severe and the joints in the neighbourhood of the involved bone are rigidly splinted by muscle spasm. The vertebral lesion may give rise to referred abdominal pain and cause confusion as in *Case* 1. Radiation to the buttock and thigh may simulate pain from a prolapsed intervertebral disk, and the narrowing of the disk space seen in early radiographs lend weight to an incorrect diagnosis.

It is essential to have repeated X-ray examinations in suspected cases, and from the ready way in which these lesions heal spontaneously it is tempting to suggest that if this is not done cases may be overlooked altogether.

DIAGNOSIS

This rests primarily on the occurrence of pain and limitation of movement of the spine or hip in association with urinary tract infection and operations on the bladder, prostate, and urethra, and secondarily on radiographic changes. These occur only after some weeks of pain and follow a quite definite pattern. In the spinal lesions the earliest feature is narrowing of the disk space; this is followed by loss of trabeculation and rarefaction of the adjacent vertebral bodies, there being almost without exception at least two vertebræ involved in the process. Later still, a definite cavity appears and thereafter there may be complete or partial collapse of the vertebral bodies, with, as in *Case* 2, possible compression of the spinal cord.

The differentiation from tuberculosis at this stage is extremely difficult, but within a few weeks new bone will be seen appearing around the cavity. This process develops rapidly and leads to much lateral bridging between the vertebræ involved, producing a characteristic parrot-beak appearance. These features readily distinguish the disease from tuberculosis and also from metastasis, this last being an obvious differential point in cases of prostatic enlargement.

The radiographic changes in the hip-joint begin with narrowing of the joint space and rarefaction of the femoral head, followed in most cases by the latter's complete destruction, and finally comparatively rapid healing with much new bone formation.

The average time taken for healing in the cases reviewed was between six and seven months.

The laboratory investigations seldom help greatly in diagnosis. The white-cell count is not always raised, though a high erythrocyte sedimentation rate is a constant feature. The blood-culture may be positive in the acute febrile stage, but is by no means always so, presumably because this is a local venous bacteræmia and not a systemic one.

Henson and Coventry (1956) confirmed five of their seven cases by needle biopsy of the affected vertebræ and advocate this as a safe and reliable procedure.

TREATMENT

The lesions, whether of the vertebræ or hip-joints, heal readily with immobilization. It would seem important to eradicate the urinary infection wherever possible, for not only will the successful antibiotic be likely to benefit the bone lesion but the risk of multiple lesions occurring, as in *Case* 3, will be lessened. It is usual to find that the urinary organisms are resistant to many of the antibiotics and recourse must be made to the more recently developed drugs such as those of the tetracycline group. Achromycin has proved beneficial in osteitis pubis and may therefore be equally useful in other skeletal lesions. It is of prime importance to improve the general health of the patient, who is often debilitated and anæmic, by all the measures available. Anæmia, if severe, should be corrected by blood transfusion, and the inclusion of adequate supplies of vitamins and minerals in the diet should not be overlooked. Where the pain is severe much relief is afforded by local heat or by short-wave diathermy.

DISCUSSION

The close relationship between the operation and the onset of pain in the affected bone or joint leaves little room for doubt that they are cause and effect. This conception is strengthened by the invariable existence of a urinary infection and by the cases where bone biopsy has shown the presence of organisms common to the urinary tract.

In all six cases presented the urine was heavily infected often with two or more organisms. Debilitation, particularly profound anæmia, plays a definite role in the development of these lesions. This is consistent with the conception of a low-grade osteomyelitis caused by an organism of moderate or low virulence.

The close resemblance of the bone lesions in their radiographic appearance and their behaviour to osteitis pubis is striking. In that condition there is initially destruction of the cartilage of the symphysis with resultant widening of the gap between the pubic bones, followed by rarefaction of the bones themselves, and finally healing with much new bone formation, suppuration being almost unknown.

Beneventi and Noback (1950), following Batson's technique, have shown the communication between the venous drainage of the symphysis pubis and the prostatic venous plexus. Mortensen (1951), commenting on the possibility that a combination of low-grade infection and venous thrombosis may be the cause of osteitis pubis, interestingly mentions two cases in which the pubic lesion was associated with a similar lesion in the spine.

Case 3 shows only a spinal lesion associated with osteitis pubis but a lesion in the left femoral head as well.

That venous thrombosis may play a major part in the development of all these lesions is very probable. The flow in the paravertebral venous system is extremely sluggish and ideally suited to the development of thrombi. The lesions themselves, both in appearance at autopsy and in their behaviour in life, have features more akin to an avascular necrosis in some respects than an infective process, though elements of both processes are present. This may explain why suppuration is so uncommon.

It seems reasonable to suppose that there is a common mechanism in the production of all these bone lesions, and that after gaining access to the highly complex and diffuse venous network already described, the organisms produce a venous thrombosis and a low-grade osteomyelitis in the affected area.

The lessons to be gained from these cases are that operations on the urinary tract in the presence of infection are to be avoided whenever possible; the lowering of patients' resistance, particularly by anæmia, favours the development of these bone lesions; increased intra-abdominal pressure, be it due to gaseous distension or chronic cough, may theoretically help in their causation, and finally pain in the back or hip after pelvic operations should be investigated with some caution and not dismissed on a single X-ray examination.

SUMMARY

Five cases of osteomyelitis following operations on the lower urinary tract, and one occurring spontaneously in the presence of urinary infection, are

presented. The sites involved were spine alone, 3 cases; spine, pubis, and left hip, 1 case; hip alone, 1 case; and shoulder alone, 1 case.

The paravertebral venous plexus and its branches are suggested as the probable pathway by which the organisms reach the bones involved; the pathology, diagnosis, and treatment of the lesions are discussed and the literature on the subject is reviewed.

The relationship of these bone lesions to osteitis pubis and the similarity between the two conditions is stressed, and a possible common aetiology is advanced.

I am greatly indebted to Mr. H. L.-C. Wood and Mr. J. G. Yates-Bell for their help and advice in the preparation of this paper, and my thanks are due to them, to Mr. Harland Ress, and to Mr. A. W. Badenoch for permission to publish details of their cases. I also thank Mr. W. Smith of the Photographic Department of King's College Hospital, and Mr. E. Wilson of the Photographic Unit of the Royal Society of Medicine, for the illustrations.

REFERENCES

ALDERMAN, E. J., and DUFF, J. (1952), *J. Amer. med. Ass.*, **148**, 283.
BATSON, O. V. (1940), *Ann. Surg.*, **112**, 138.
BENEVENTI, F. A., and NOBACK, G. J. (1950), *J. Urol.*, **62**, 663.
BRESCHET, G. (1832), *Recherches anatomiques, physiologiques et pathologiques sur le système veineux, et spécialement sur les canaux veineux des os.* Paris: Engelmann.
CARSON, H. W. (1931), *Brit. J. Surg.*, **18**, 400.
CHRICHTON, E. P., and HAMMAN, H. A. (1953), *Canad. med. Ass. J.*, **69**, 529.
DE FEO, E. (1954), *Radiology*, **62**, 396.
DEMING, C. L., and ZAFF, F. (1943), *Trans. Amer. Ass. gen.-urin. Surg.*, **35**, 287.
DONAHUE, C. D. (1949), *J. Urol.*, **61**, 405.
FLEMMING, C. (1935), *Proc. R. Soc. Med.*, **28**, 897.
HENSON, S. W., and COVENTRY, M. B. (1956), *Surg. Gynec. Obstet.*, **102**, 207.
HURWITZ, A., and ALBERTSON, H. A. (1950), *New Engl. J. Med.*, **243**, 562.
KRETSCHMER, J. L., and OCKULY, E. A. (1935), *J. Urol.*, **34**, 142.
KULOWSKI, J. (1936), *J. Bone Jt Surg.*, **18**, 343.
KUSUNOKI, T. (1938), *Z. Urol.*, **32**, 699.
LABYERIE, G. (1905), *Gaz. Hôp., Paris*, **78**, 1143.
LAME, E. L. (1956), *Amer. J. Roentgenol.*, **75**, 938.
LANNELONGUE, O. M. (1897), "On Acute Osteomyelitis". *Miscellaneous, Pathological, and Practical Medicine Tracts*, 976. Paris.
LEIGH, T. F., KELLY, R. P., and WEENS, H. S. (1955), *Radiology*, **65**, 334.
LIMING, R. W., and YOUNGS, F. J. (1956), *Ibid.*, **67**, 92.
MORTENSEN, H. (1951), *Aust. N.Z. J. Surg.*, **21**, 103.
MUSSEY, R. D. (1954), *Illinois. med. J.*, **105**, 253.
PEDERSEN, V. C. (1922), *J. Urol.*, **7**, 405.
QUAIN, J. (1837), *Elements of Anatomy*, 622. London: Taylor & Walton.
RIBET, M. (1926), *Les artères ostéoarticulaires.* Algiers: Imprimerie Moderne.
SCHEIN, A. J. (1940), *Arch. Surg., Chicago*, **41**, 750.
SELIG, S. (1934), *J. Bone Jt Surg.*, **16**, 189.
SILVER, C. M. (1941), *Bull. Hosp. Jt Dis.*, **2**, 10.
STOTZ (1938), *Zbl. Chir.*, **65**, 53.
WILSON, T. H. (1935), *Proc. R. Soc. Med.*, **28**, 902.
WOOD, H. L.-C. (1954), *Ibid.*, **47**, 927.

CONGENITAL INTRINSIC DUODENAL STENOSIS PRESENTING AFTER INFANCY

A REVIEW OF RECORDED CASES AND REPORT OF A CASE SHOWING DUODENO-HEPATIC REFLUX

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CONGENITAL intrinsic duodenal stenosis seen in the early weeks of life is a well recognized surgical emergency. Cases first seen after infancy are rare and present a diagnostic problem, as the possibility of a congenital lesion is apt to be overlooked. A review of 26 recorded cases (*Table I*) is presented and we report a case in which duodeno-hepatic reflux was demonstrated pre-operatively by barium meal.

CLASSIFICATION OF TYPES

Atresia is not considered, as this is found in infancy only. Descriptions of its forms have been given by Forssner (1907), Spriggs (1910, 1912), and others.

For the stenosing form of obstruction we suggest a simple classification (*Fig.* 34) into three types. In one, the lumen of the duodenum is obstructed by a septum, and in a second by narrowing of the duodenal wall; the former (A) we term perforated septum and the latter (B) mural stenosis. The possibility of a third combined form (C) exists. Review of the literature suggests that perforated septum is the commonest lesion. The septum is composed of the bowel coats, commonly with the exception of the submucosa, while the muscle coat may be so rudimentary that many regard the septum as membranous. Mural stenosis is less common. In this form there is narrowing of an isolated segment of the duodenum, generally with no evidence of fibrosis, since the lesion is congenital. The fibrosis noted in Bonar's (1935) case was considered to be due to ischæmia, and the presence of an abnormal entrance of the bile-duct supported his belief that the lesion was congenital.

The possibility of a combined form of stenosis is suggested by the case of Terry and Kilgore (1916). Here a definite narrowing of bowel was noted at operation with constriction to a third or less of the normal diameter for a distance of 1·5 cm., while at autopsy the constriction was complicated by an obstructing fold of duodenum.

Only transverse septal folds would be expected to cause obstruction, but vertical folds have been

described (Calder, 1733; Wilkie, 1913). In Wilkie's case both transverse and vertical folds were present. This author also mentioned that he had seen three other adult autopsies where transverse septa were present, but gave no other details.

Table I.—TWENTY-SIX CASES OF CONGENITAL INTRINSIC DUODENAL STENOSIS PRESENTING AFTER INFANCY

AUTHOR AND DATE	AGE	TYPE	APERTURE	OPERATION	CONFIRMATION		DURATION OF HISTORY	PRELIMINARY DIAGNOSIS
					Operation	Autopsy		
Buchanan, 1861	18 mth.	P.S.*	2·5 mm.	—	—	Yes	Short	Brain injury
Moore, 1884	40 yr.	P.S.	10–15 mm.	—	—	Yes	—	Nil — no symptoms. Death from bronchitis
Silcock, 1885	34 yr.	P.S.	15 mm.	—	—	Yes	—	Nil—no history given. Death from cancer of colon
Hutton, 1898	35 yr.	P.S.	?	—	—	Yes	Long	Nil
Seidlin, 1907	2½ yr.	P.S.	7 mm.	—	—	Yes	Short	Acute intestinal obstruction
Keith, 1910	Adult	P.S.	?	—	—	Yes	?	?
Wilkie, 1913	58 yr.	P.S.	?	—	—	Yes	None	Nil—Death from acute pancreatitis
Terry and Kilgore, 1916	24 yr.	P.S.	?	Gastro-enterostomy	Yes	Yes	Long	Pyloric stenosis
Cautley, 1919	1 yr.	M.S.†	3 mm. approx.	Laparotomy	Yes	Yes	Long	Pyloric stenosis
Nagel, 1925	72 yr.	P.S.	8 mm.	Laparotomy	No	Yes	None related	Intestinal obstruction
Cannon and Halpert, 1929	8 yr.	P.S.	4 mm.	—	—	Yes	Long	Pneumoperitoneum
Gordon, 1930	21 yr.	M.S.	3 mm.	Laparotomy	Yes	Yes	Long	Acute intestinal obstruction
Ladd, 1932	14 mth.	P.S. ?	?	Duodeno-jejunostomy	Yes	None	Short	Duodenal obstruction
„ 1933	8 yr.	M.S.	?	Duodeno-jejunostomy	Yes	None	Short	Duodenal stenosis
Bonar, 1935	13 mth.	M.S.	Nil	Gastro-jejunostomy	Yes	Yes	Short	Duodenal obstruction
Kreig, 1937	36 yr.	P.S.	8 mm.	Gastro-jejunostomy	Yes	None	Long	Intestinal obstruction
Braun (2 cases), 1938	1½ yr.	P.S.	8 mm.	—	—	Yes	Long	Diabetic coma?
	49 yr.	P.S.	6 mm.	—	—	Yes	Long	Mesenteric thrombosis
Nagel, 1939	1 yr.	P.S.	12–15 mm.	Duodeno-jejunostomy	Yes	—	Long	Duodenal obstruction
Saunders and Lindner, 1940	7½ yr.	P.S.	8 mm.	Excision	Yes	None	Long	Duodenal obstruction
Nelson, 1947	26 yr.	P.S.	10 mm.	Excision and gastro-jejunostomy	Yes	—	Short	Duodenal septum
Lamson, 1946	28 yr.	P.S.	18 mm. approx.	Excision and duodeno-jejunostomy	Yes	None	Long	Congenital duodenal obstruction
St. John and Tamoney, 1952	2 yr.	P.S.	3 mm. approx.	Duodeno-duodeno-stomy	Yes	None	Long	Congenital duodenal diaphragm
Louw, 1952	7½ yr.	P.S.	5 mm.	Ladd's operation	No	Yes	Long	Duodenal obstruction
Bill and Pope, 1954	15 mth.	P.S.	5 mm.	Incised septum	Yes	None	Long	Duodenal obstruction
Madden and McCann, 1956	10 yr.	P.S.	3 mm. approx.	Duodeno-duodeno-stomy	Yes	None	Long	Congenital duodenal obstruction

* P.S. = perforated septum. † M.S. = mural stenosis.

AETIOLOGY

In considering intrinsic occlusion of the duodenum the theory of failure in the resolution of proliferated epithelial cells is the most acceptable. This failure was suggested by Tandler (1900), and in conjunction with Sutton's (1889) observation that occlusions of the alimentary tract usually occur at the site of an "embryological event" would afford an explanation of the type and site of the occlusion. The commonest site is in the region of the ampulla of Vater—the site of junction of the foregut and midgut. The next commonest site at the duodeno-jejunal flexure may be analogous if we accept the change in the attachment and development of the mesentery as being such an "event". Tandler's theory was elaborated by Forssner (1907), who wrote of two processes occurring in harmony—a dissolution of the epithelial occlusion plus an infolding process of

the mesenchyme. He thought that the lesions resulted from disharmony in these processes.

The theory of developmental failure is further emphasized by the finding of other congenital defects in association—imperforate anus and absence of organs (Cordes, 1901), and the presence of Mongolism. Louw (1952) found 9 out of 31 cases to be

FIG. 34.—Classification of type. A, Perforated septum. B Mural stenosis. C Possible combined form.

FIG. 35.—Barium meal demonstrates a narrowing of the second part of the duodenum in the region of the entrance of the common bile-duct with reflux of barium into the biliary tree and gall-bladder.

Mongols. In Cautley's (1919) case Mongolism was suggested but its presence not fully substantiated.

Recent attention has been focused on the possibility of a primary vascular deficiency being responsible for the developmental failure. This theory followed the observation by Wyss (1900) of the absence of the pancreatico-duodenal artery in 2 cases of duodenal atresia. Durante (1901) and Taillens (1903) suggested that this vascular abnormality might be secondary to intra-uterine infection. Louw and Barnard (1955) have given further support to this theory. They have produced intestinal atresia experimentally by ligating the artery to a segment of bowel in the fœtus of a dog.

Spriggs (1912) reviewed the many theories propounded and classified them in three groups in order of frequency: (1) Developmental defects. (2) Fœtal accidents. (3) Fœtal diseases.

CASE REPORT

The patient was a 45-year-old Pakistani seaman. He was well and symptom-free until three months before admission to hospital on March 1, 1953. Then following a meal of goat's liver, he suddenly developed vomiting, heartburn, and nausea, with acid regurgitation. Frequent attacks of vomiting continued, of foodstuffs and bile, sometimes streaked with blood. There was associated flatulence, abdominal distension, and he lost weight steadily. There was no diarrhœa. His symptoms improved on a self-imposed liquid diet, but he felt easily tired and unable to work.

On admission he was severely emaciated (weight 84 lb.). No abdominal mass or tenderness was noted. There was gross dental caries. From time to time he developed upper abdominal distension with visible peristalsis and effortless vomiting, and he continued to complain of epigastric discomfort.

INVESTIGATIONS.—Hb was 9·0 g. per 100 ml. The blood-picture was one of normochromic, normocytic anæmia. W.B.C. 4700 per c.mm. Eosinophils 705 per c.mm. (15 per cent). Plasma albumin 3·6 g. per 100 ml.; globulin 4·4 g. per 100 ml. Blood W.R. negative. Radiograph of chest, normal. Stools: repeated examinations demonstrated ova of *Ankylostoma duodenale* on one occasion only. Barium meal (March 3) (*Fig.* 35) demonstrated a narrowing of the second part of the duodenum in the region of the entrance of the common bile-duct with reflux of barium into the biliary tree and gall-bladder.

FIG. 36.—At operation narrowing of the duodenum is demonstrated, the site being indicated by forceps.

Barium passed through the duodenum without delay. Air in the biliary tract was evident on the early films.

AT OPERATION (April 23, Mr. F. R. Brown).—The stomach wall was hypertrophied, the pylorus relaxed. The duodenum narrowed suddenly at a point about 3 in. from the pylorus (*Fig.* 36), the external diameter of the proximal part being 1 in., and of the constriction about ½ in. The common bile-duct and pancreatic duct entered the duodenum at the proximal end of the constricted portion. A small lobe of pancreatic tissue adhered to the anterolateral aspect of the duodenum beyond the constriction, but appeared to cause no pressure effect and there was no evidence of an annular pancreas or of fibrosis in the region of the ampulla of Vater. Distal to this the duodenum was normal in appearance, and liver

spleen, common bile-duct, and gall-bladder all appeared normal. The operative diagnosis was congenital intrinsic stenosis of the duodenum. A retrocolic gastro-jejunostomy was performed.

Post-operative progress was uneventful and there was no further vomiting or heartburn. Barium meal nineteen days after operation showed the gastro-enterostomy to be functioning, but some barium passed through the duodenum and the biliary tract was outlined as before. Three months after operation the patient's weight was 105 lb. At this time a cholecystogram showed no gall-bladder function. The patient was seen one year later, asymptomatic, feeling fit, and having returned to his former occupation as a stoker. He was back to his normal weight of 115 lb. A repeat barium meal (Feb. 1, 1955) almost two years later showed a functioning gastro-enterostomy again with reflux of barium into the biliary tract.

CLINICAL FEATURES

These have been described for cases occurring in infancy by Cordes (1901), Spriggs (1912), Davis and Poynter (1922), Louw (1952), and others.

In adults there is no characteristic clinical picture. The cases reviewed fall into three groups. One is asymptomatic, the lesion being found unexpectedly at operation. In the other two the clinical features are similar, differing only in length of history, which may be of recent or of long standing, and intermittent attacks of intestinal obstruction. These main features are epigastric pain, nausea, vomiting—often with relief of pain, and sometimes gastric distension and borborygmi. The accepted cause of symptoms is blockage of the aperture in the septum by a bolus of food and symptoms persist until the bolus has passed on or been digested. Buchanan (1861) described a case in which relief was obtained by taking a liquid diet and this was also noted in our case. The aperture is often, but not always, eccentric in position. The presence of an eccentric aperture, particularly in the superior portion of the septum, was the reason given by Lamson (1946) for the absence of acute obstruction in his case.

In considering why recurrence of obstruction should occur in some cases, it is possible that inability of the aperture to distend and allow onward passage of food is a factor responsible, and the late occurrence of symptoms could be due to a secondary fibrosis of the margins of the aperture. We have not been able to find, however, any histological reports of fibrosis in the literature on these cases.

DIAGNOSIS

The diagnosis of intrinsic duodenal obstruction in the adult is difficult. In infancy the thought of a congenital lesion comes easily to mind, but in the older age-groups pyloric stenosis, inflammatory fibrosis, tumour, and intussusception are more often suspected. Barium-meal examination is helpful in demonstrating the site of the lesion but not the cause. When the history is long, and radiographic examination shows an obstruction, a congenital cause should be considered. In some cases, however (St. John and Tamoney, 1952; Kreig, 1937), barium-meal examination was negative; in these laparotomy alone may be diagnostic. Even then the diagnosis may not be obvious as the presence of distension proximal to the lesion is variable, and there may be no depression in the duodenal wall to suggest a septum. In such cases exploration of the duodenum through an enterostomy incision is necessary to demonstrate the lesion.

When narrowing of the duodenum is present as in mural stenosis, its congenital nature is suggested by the absence of any definite pathological lesion such as tumour, ulcer, or fibrosis due to a previous inflammatory lesion.

TREATMENT

The operations suggested in the treatment of congenital intrinsic duodenal obstruction have been illustrated by Madden and McCann (1956) and are as follows:—

1. Direct operations: (*a*) Excision of the septum. (*b*) Incision of the septum.

2. Short-circuit operations; (*a*) Duodeno-duodenostomy. (*b*) Duodeno-jejunostomy. (*c*) Gastro-jejunostomy.

The direct operations are to be preferred, especially in adults, but if great thinning of the wall of the duodenum has occurred, making suturing hazardous, then the short-circuit gastro-enterostomy may be safer. The only fault of the latter is that adequate drainage of the duodenum is not obtained.

In reviewing these cases one is struck by the possibility that some listed as chronic duodenal ileus may in fact have a duodenal septum with a large aperture.

Duodeno-hepatic Reflux.—We have found no previous record of duodeno-hepatic reflux due to congenital duodenal stenosis. The biliary tract may be outlined during a barium meal as a result of fistula, or less commonly from reflux into the common bile-duct due to incompetence of the sphincter of Oddi. Our case is one of reflux complicating intrinsic duodenal stenosis of congenital origin, presumably mural in type.

It is of interest that our patient gave no previous history of acute cholecystitis, cholangitis, or jaundice despite the fact that long-standing incompetence of the sphincter of Oddi is likely to have been present. This would suggest that incompetence, *per se*, is not a cause of so-called 'ascending infection' of the biliary tract, but that obstruction is the main aetiological factor.

SUMMARY

A case of congenital intrinsic duodenal stenosis in a 45-year-old male is recorded in which duodeno-hepatic reflux was obtained at pre-operative barium meal.

The literature of 26 recorded cases presenting after infancy is reviewed; in none of these was duodeno-hepatic reflux found.

The aetiology, clinical features, diagnosis, and treatment of the condition are discussed.

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REFERENCES

BILL, A. H., and POPE, W. M. (1954), *Surgery*, **35**, 482.
BONAR, T. G. D. (1935), *Lancet*, **2**, 822.
BRAUN, H. (1938), *Virchows Arch.*, **302**, 618.
BUCHANAN, G. (1861), *Trans. path. Soc. London*, **12**, 121.
CALDER, J. (1733), *Medical Essays and Observations, Edin.*, **1**, 203.
CANNON, P. R., and HALPERT, B. (1929), *Arch. Path. (Lab. Med.)*, **8**, 611.
CAUTLEY, F. (1919), *Brit. J. Child. Dis.*, **16**, 65.
CORDES, L. (1901), *Arch. Pediat.*, **18**, 401.
DAVIS, D. L., and POYNTER, C. W. (1922), *Surg. Gynec. Obstet.*, **34**, 35.
DURANTE, G. (1901), *Bull. Soc. Anat. Paris*, **3**, 593.
FORSSNER, H. (1907), *Anatomische Hefte*, **34**, 4.
GORDON, L. (1930), *Brit. J. Surg.*, **18**, 331.
HUTTON, W. F. (1898), *Edinb. Hosp. Rep.*, **5**, 7.
KEITH, A. (1910), *Brit. med. J.*, **1**, 301.
KREIG, E. G. (1937), *Ann. Surg.*, **106**, 33.
LADD, W. E. (1932), *New Engl. J. Med.*, **206**, 277.
— — (1933), *J. Amer. med. Ass.*, **101**, 1453.
LAMSON, O. F. (1946), *West. J. Surg.*, **54**, 384.
LOUW, J. H. (1952), *S. Afr. J. clin. Sci.*, **3**, 109.
LOUW, J. H., and BARNARD, C. N. (1955), *Lancet*, 1 1065.
MADDEN, J. L., and MCCANN, W. J. (1956), *Int. Abstr. Surg.*, **103**, 1.
MOORE, N. (1884), *Trans. path. Soc. Lond.*, **35**, 202.
NAGEL, C. E. (1939), *J. int. Coll. Surg.*, **2**, 315.
NAGEL, G. W. (1925), *Arch. Surg., Chicago*, **11**, 529.
NELSON, W. I. (1949), *Minnesota Med.*, **30**, 745.
ST. JOHN, L. A., and TAMONEY, H. T. (1952), *Amer. J. Dis. Child.*, **84**, 439.
SAUNDERS, J. B. de C. M., and LINDNER, H. H. (1940), *Ann. Surg.*, **112**, 321.
SEIDLIN, S. M. (1907), *Arch. Pediat.*, **24**, 813.
SILCOCK, A. R. (1885), *Trans. path. Soc. Lond.*, **36**, 207.
SPRIGGS, N. I. (1910), *Lancet*, **1**, 94.
— — (1912), *Guy's Hosp. Rep.*, **66**, 143.
SUTTON, J. B. (1889), *Amer. J. med. Sci.*, **98**, 457.
TAILLENS (1903), *Rev. méd. Suisserom.*, **23**, 168.
TANDLER, J. (1900), *Morph. Jb.*, **29**, 187.
TERRY, W. I., KILGORE, A. R. (1916), *J. Amer. med. Ass.* **66**, 1774.
WILKIE, D. P. D. (1913), *Edin. med. J.*, **11**, 219.
WYSS, M. O. (1900), *Bruns Beitr. klin. Chir.*, **26**, 631.

APPENDICULAR GRANULOMA

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THIS paper is based on a group of cases of an unusual type of appendicitis, which is quite distinct from the ordinary form of the disease both in its pathology and clinical course. Pathologically it is characterized by an excessive production of granulation and fibrous tissue, and clinically it resembles carcinoma of the cæcum.

FIG. 37.—*Case* 1. Barium enema showing a small filling defect in the cæcum.

CASE REPORTS

Case 1.—Mrs. J. R., aged 55, admitted Oct. 31, 1953. The patient had noticed rumbling noises and intermittent discomfort in the abdomen for one year and had also lo weight. Her bowels were opened normally each da and there had been no vomiting or disturbance of micturition. The abdomen was distended and occasional bor borygmi could be heard without the aid of a stethoscope but no tumour was palpable. On rectal examination small, firm, fixed mass could be felt on the right side the pelvis. The heart and lungs were normal and th blood-pressure was 170/90. There was an evening rise of temperature to between 99 and 100° F. On plain

FIG. 38.—*Case* 1. Excretion urogram. The calcified mass in the right half of the pelvis (later found to consist of two appendicular concretions) is associated with a minor degree of ureteric stasis.

radiographs of the abdomen several dilated loops of sma intestine and a number of fluid levels were seen. barium enema (*Fig.* 37) showed a small filling defe in the cæcum, and a diagnosis of intestinal obstruction du to carcinoma of the cæcum was made.

FIRST OPERATION (Nov. 5, 1953).—Through a right lower paramedian incision a mass was found at the ileocæcal angle. Most of the swelling lay in the pelvis, to the wall of which it was firmly attached. A side-to-side anastomosis was carried out between the dilated lower ileum and the collapsed transverse colon.

Beginning 2 days before the operation the patient was given penicillin, 800,000 units daily for 2 weeks, and streptomycin, 2 g. daily for 5 days. An excretion urogram

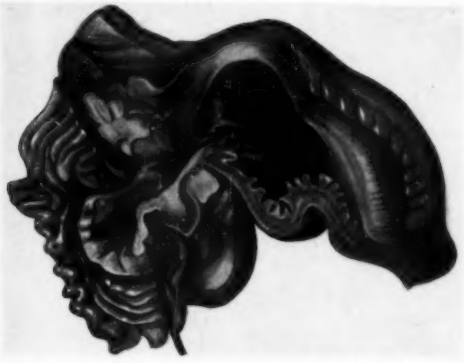

FIG. 39.—*Case* 1. Ileocæcal junction seen from in front, showing the stenosed terminal ileum with œdematous mucosa prolapsing into the cæcum. Probe passed into orifice of appendix.

FIG. 41.—*Case* 1. Ileocæcal junction from below. The appendix is buried in the thick fibrous wall of the terminal part of the ileum.

(*Fig.* 38) showed a small, irregularly calcified body in the pelvis on the right-hand side, which was causing some stasis in the right ureter, but both kidneys had a normal appearance and function. On cystoscopy the bladder wall was seen to bulge inwards in a position corresponding to the calcified mass, but the mucous membrane appeared normal. The hæmoglobin was 13·6 g. per 100 c.c. (92 per cent) and tests of the stools for occult blood were consistently negative.

SECOND OPERATION.—The patient would not consent to this until April 26, 1954. An oblique incision was made in the right lower quadrant of the abdomen and the previous findings were confirmed. Mobilization of the mass was begun from the lateral side and it was separated from the right ureter. The mass was then found to

FIG. 40.—*Case* 1. Ileocæcal junction from behind. The lumen of the proximal part of the appendix forms a thick-walled cavity.

consist of two portions, an upper and larger part at the ileocæcal junction connected by a narrow bridge of tissue to a lower and smaller part, which was approximately 1 in. (2·5 cm.) in diameter and was firmly fixed to the lateral pelvic wall near the bladder. As the lower part

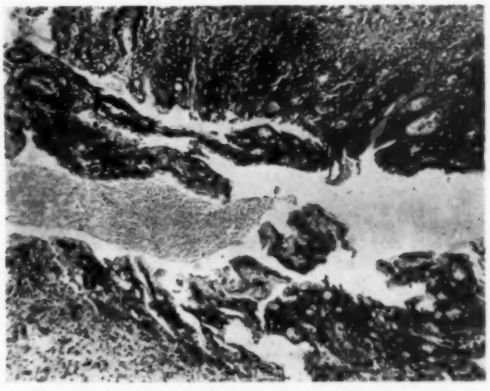

FIG. 42.—*Case* 1. Wall of cavity behind ileocæcal junction showing remnants of appendicular mucosa. (× 72.)

could not be freed the connecting bridge was divided, whereupon a concretion ½ in. (1·25 cm.) in diameter escaped from the deep surface of the upper portion. Right hemicolectomy was then completed without further difficulty.

SPECIMEN.—On opening the cæcum (*Fig.* 39) a prominent swelling measuring ¾ in. (2·0 cm.) in all diameters was seen at the site of the ileocæcal valve. The ileum opened at the summit of this projection, which consisted of prolapsed, œdematous, and thickened mucous membrane only. Laying open the ileum showed that

the lumen of its terminal part was reduced to an extremely narrow channel by dense fibrosis of its walls. The stricture measured 1½ in. (3·0 cm.) in length and terminated distally at the base of the intracæcal projection. Above the stricture the ileum was much dilated and hypertrophied. At the posterior aspect of the ileocæcal junction (*Fig.* 40) was a cavity with thick, fibrous walls from which the concretion was extruded at operation and from

FIG. 43.—*Case* 2. Barium follow-through showing compression of terminal ileum and cæcum with preservation of normal mucosal folds.

FIG. 45.—*Case* 2. Wall of retrocæcal abscess showing remnants of appendicular mucosa embedded in granulation tissue. (× 72.)

which a second smaller concretion was now removed. The lumen of the cavity measured approximately ½ in. (1·25 cm.) in diameter, and its anterior wall formed the proximal part of the posterior wall of the ileal stricture (*Fig.* 41). Posterior to the distal part of the stricture was a thick-walled, funnel-shaped portion of cæcum with the orifice of the appendix at its apex. On passing a probe from the cæcum through the orifice of the appendix its point immediately emerged into the cavity, which appeared to consist of the distended lumen of the proximal part of the appendix. Presumably the appendix had first passed upwards behind the ileocæcal junction and then turned downwards to reach the pelvis, where its distal part had been left behind at operation.

HISTOLOGY.—In the region of the stricture the ileal mucosa was chronically inflamed, with numerous plasma cells and eosinophils, and with prominent lymphatic follicles. The submucosa consisted of dense fibrous tissue infiltrated by inflammatory cells. The muscular coat was hypertrophied and there was an excess of fibrous tissue with patches of inflammatory cells. The wall of the cavity lying behind the ileocæcal junction was formed by sclerotic fibrous tissue. Its inner surface was lined by necrotic material infiltrated by polymorphs, but there were also some remnants of chronically inflamed appendicular mucosa (*Fig.* 42). The histology was that of a chronic appendicular abscess.

FIG. 44.—*Case* 2. The probe is in the orifice of the appendix. The small track opening below the ileocæcal valve leads directly into a retrocæcal abscess cavity.

Case 2.—Mr. M. F., aged 76, admitted March 6, 1954. Pain in the right lower abdomen and diarrhœa had been present for 5 days, and vomiting had occurred twice soon after the onset. Dyspepsia and bronchitis had caused trouble for many years, and recently there had been swelling of the ankles and nocturnal dyspnœa. Physical examination showed a hard fixed tender mass with an irregular surface in the right iliac fossa. The liver was a little enlarged but smooth, and nothing abnormal was felt on rectal examination. The heart was enlarged and the blood-pressure was 170/80. The chest was emphysematous and many adventitious sounds were heard. The temperature rose occasionally to 99° F. A barium meal showed no abnormality in the upper alimentary tract; on follow-through examination (*Fig.* 43) it was seen that the terminal ileum was stretched around the tumour and that the cæcum did not fill. In both small and large bowel there were normal mucosal folds at the periphery of the mass. Three specimens of fæces examined for occult blood were weakly positive, negative, and positive respectively. The hæmoglobin was 14·1 g. per 100 c.c. (95 per cent) and the white blood-count 7200 per c.mm. (polymorphs 80 per cent, lymphocytes 15 per cent, and monocytes 5 per cent). The urine contained 50 mg. of protein per 100 c.c. and an occasional leucocyte; it gave a scanty growth of *Staphylococcus albus* on culture. An excretion urogram was normal. Three weeks after admission, during which time no antibiotics had been given, the abdominal mass was unchanged in character and operation was advised.

AT OPERATION.—A right paramedian incision was made and a hard, fixed swelling was felt in the posterior wall of the cæcum. After mobilization of the cæcum from the posterior abdominal wall the base and tip of the appendix were identified; the remainder of the appendix was incorporated in the mass, from which it could not be freed. A right hemicolectomy was performed followed by ileotransverse anastomosis.

After making good progress for seven days following the operation, the patient died of acute pulmonary œdema.

SPECIMEN.—On opening the bowel along its anterior aspect the only abnormality to be seen was a small round raised red area in the mucous membrane of the cæcum (*Fig.* 44). It lay immediately below the ileocæcal valve, between the valve and the orifice of the appendix, and measured $\frac{1}{16}$ in. (8 mm.) in diameter. On its summit there was a small orifice. The appendix was short, and after running upwards behind the cæcum for rather less than 1 in. (2·5 cm.) it turned medially and doubled back so that its tip lay alongside its base. A lumen could be found in the proximal part of the appendix only; it led into a thick-walled cavity lying between the middle portion of the appendix and the posterior wall of the cæcum. The cavity had a rough red lining and an internal diameter of approximately $\frac{1}{2}$ in. (1·25 cm.). The small opening found in the cæcal mucous membrane led directly backwards into the cavity by a narrow track. In this area, where it formed the anterior boundary of the cavity, the cæcal wall was infiltrated with fibrous tissue, particularly in the submucous layer, and it was approximately $\frac{3}{4}$ in. (1·0 cm.) thick.

HISTOLOGY.—The cavity in the retrocæcal region was a chronic abscess lined by granulation tissue in which there were numerous blood-capillaries and polymorphs, and the sinus in the cæcum led to it. In the wall of the abscess remnants of the appendix were present (*Fig.* 45). They consisted of fragments of inflamed mucosa and muscular coat infiltrated by chronic inflammatory cells and polymorphs. There was no evidence of malignancy.

Case 3.—Miss I. M., aged 74, admitted June 12, 1952. For two months there had been persistent pain in the right lower abdomen. It had begun gradually and had at times radiated to the inner aspect of the right thigh. The bowels were regular and no blood had been passed. There had been no loss of weight. A hard fixed slightly tender mass, about the size of a golf ball, was felt in the right iliac fossa. Rectal examination was negative. Nothing abnormal was found in the heart and lungs, and the blood-pressure was 160/80. A barium enema showed no abnormality apart from mild diverticulosis of the pelvic colon, and an excretion urogram was normal. Two specimens of fæces examined for occult blood were reported as weakly positive and negative respectively. The hæmoglobin was 13·1 g. per 100 c.c. (89 per cent) and the red blood-cells were 4,600,000 per c.mm. Three weeks after admission the abdominal tumour was unchanged. There had been no rise of temperature and no antibiotics had been given.

AT OPERATION.—The mass was situated in the posterior wall of the cæcum and was fixed to the posterior abdominal wall. After mobilizing the cæcum with considerable difficulty, a small but extremely hard retrocæcal appendix was found to be incorporated in the mass. The appendix could not be separated from the cæcum and, as malignancy could not be ruled out, a right hemicolectomy was performed.

PATHOLOGY.—The appendix was 2 in. (5·0 cm.) in length and $\frac{3}{4}$ in. (1·0 cm.) in diameter. It was surrounded by fibrous fatty tissue and was firmly adherent to the posterior wall of the cæcum, which in this region was infiltrated by fibrous tissue and was $\frac{3}{4}$ in. (1·0 cm.) thick. There was a small ulcer in the mucous membrane of the cæcum overlying the thickened area.

Sections showed the appendix with a small lumen and lined by an atrophic mucosa almost without lymphatic tissue. The submucosa was thick and formed of dense fibrous tissue. The muscularis was well developed in two-thirds of the circumference of the appendix; in one-third it was missing and here there was a large area of granulation tissue extending through the wall of the cæcum which was ulcerated (*Fig.* 46). In the granulation tissue many foreign body giant cells were seen, some of them surrounding fragments of fæces. The appearances were those of chronic appendicitis and peri-appendicitis. The lymph-nodes showed a well-marked sinus catarrh.

Case 4.—Mrs. C. F., aged 59, admitted Feb. 1, 1954. Intermittent pain had occurred in the right iliac fossa for four months. There had been no vomiting and the bowels were regular. At the age of 20 her abdomen had been explored at St. Mary's Hospital during an attack of acute salpingitis but the appendix had not been removed, and an operation for bilateral broad ligament cysts had been performed when she was 37. In the right lower quadrant of the abdomen a fixed and tender mass could be

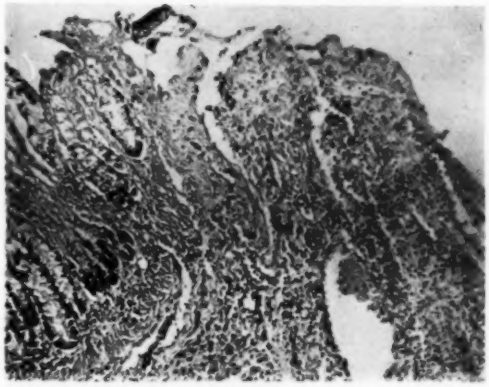

FIG. 46.—*Case* 3. Granulation tissue extending from the appendix through the cæcal wall which is ulcerated (on the right). On the left, cæcal mucosa bordering the ulcer. (× 72.)

felt. It was palpable bimanually on vaginal examination and was distinct from the uterus. There was no pyrexia. The heart and lungs were normal, and the blood-pressure was 220/120. The white blood-count was 8800 per c.mm. and the hæmoglobin was 13·2 g. per 100 c.c. (89 per cent).

A clinical diagnosis of right ovarian tumour was made and on Feb. 3, 1954, the abdomen was explored through a midline incision. The uterus and right ovary were normal, but the left ovary was absent. The mass was found to be in the posterior wall of the cæcum and ascending colon. It was adherent to the posterior abdominal wall and was thought to be a carcinoma, so a right hemicolectomy was performed. The post-operative course was uneventful.

PATHOLOGY.—In the posterior wall of the cæcum there was a firm, fibrous mass measuring $1 \times \frac{3}{4} \times \frac{3}{4}$ in. (2·5 × 2·0 × 2·0 cm.) which replaced all but the most proximal part of the appendix. The mucosal surface of the bowel was normal apart from the orifice of the appendix which was dilated and had swollen and inflamed margins. Histological examination showed that the submucosa of the remaining part of the appendix was much thickened with young fibrous tissue containing eosinophils, plasma cells, and lymphocytes, and that in the muscular layer there were scattered chronic inflammatory cells of the same type. Outside this was a much greater amount of young fibrous tissue containing a large number of similar chronic inflammatory cells. This tissue extended through the muscular coat of the cæcum into its submucosa, which was considerably thickened, and it appeared to be attaching the appendix firmly to the cæcum. The changes were those of appendicular and peri-appendicular chronic inflammation and fibrosis; there was no evidence of malignancy. The lymph-nodes showed reactive hyperplasia and sinus catarrh.

Case 5.—Mr. H. K., aged 74, admitted March 6, 1956. Ten days previously severe pain had begun suddenly in the right iliac fossa and spread across the lower abdomen. Since its onset the pain had recurred

intermittently, with diminishing severity and frequency. There had been no vomiting and the bowels had been regular. In the right upper quadrant of the abdomen there was a hard tender fixed mass; the spleen was just palpable, but the liver could not be felt. No accessible lymph-nodes were enlarged. The heart and lungs were normal, and the blood-pressure was 210/100. The hæmoglobin was 12·9 g. per 100 c.c. (87 per cent) and the white blood-count was 31,800 per c.mm. with 71 per cent lymphocytes, blood-films being suggestive of chronic lymphatic leukæmia. A barium enema showed an acute kink in the ascending colon with the cæcum lying lateral

FIG. 47.—*Case* 6. Post-evacuation film of barium enema showing filling defect in medial part of cæcum.

to the hepatic flexure, but there was no filling defect. The temperature was 101° F. on admission; it gradually subsided without the use of antibiotics but the characteristics of the mass did not alter.

AT OPERATION.—On March 16, 1956, the abdomen was explored through a right paramedian incision. The mass was adherent to the under surface of the liver and involved both the hepatic flexure and the cæcum, the latter being drawn upwards from its normal situation. The lesion was thought to be a carcinoma of the colon and a right hemicolectomy was carried out. The post-operative course was stormy because of ileus and bronchopneumonia, but the patient eventually made a satisfactory recovery.

PATHOLOGY.—The mucosa of the intestine was not grossly abnormal. Only the proximal ¾ in. (1·0 cm.) of the appendix was recognizable; beyond this it was lost in a mass of fibrous and granulation tissue involving the posterior wall of the cæcum, which here was considerably thickened. Histologically, the mass consisted of fibrous tissue and inflammatory granulation tissue with numerous small abscesses. The muscular coat of the adjacent part of the cæcum was infiltrated by inflammatory cells and the submucosa was very œdematous and in places also infiltrated. The mucosa was well preserved. In the base of the appendix the mucosa was necrotic and the muscularis showed areas of granulation tissue. The appearances were those of a peri-appendicular abscess.

Case 6.—Mrs. A. W., aged 85, admitted Sept. 29, 1956. Pain had been present in the right iliac fossa for two weeks, accompanied by occasional vomiting and persistent diarrhœa. Occupying most of the right lower abdominal quadrant was a smooth hard fixed and slightly tender mass. The hæmoglobin was 13·3 g. per 100 c.c. (90 per cent) and the white blood-count was 9600 per c.mm. (polymorphs 84 per cent, lymphocytes 16 per cent). A barium enema (*Fig.* 47) showed a small filling defect with a smooth outline in the medial part of the cæcum. During the first week after admission the temperature rose occasionally to 99·6° F., but subsequently remained normal. After four weeks the mass was appreciably smaller but was still easily palpable, so surgical treatment was advised. No antibiotics had been given up to this time.

AT OPERATION.—A hard mass was found in the posterior wall of the cæcum and the appendix could not be

FIG. 48.—*Case* 7. Barium meal showing filling defect in ascending colon. The normal mucosal folds are still present.

identified. The lesion was thought to be a carcinoma, and a right hemicolectomy was performed from which the patient made an uneventful recovery.

PATHOLOGY.—Behind the cæcum and the lower part of the ascending colon there was a mass of fibrous and granulation tissue in which the appendix was embedded. This tissue extended into the wall of the neighbouring part of the cæcum, which was considerably thickened, and it bound the appendix firmly to the cæcum. The proximal part of the appendix was lined by reddened mucous membrane, but the distal part was lined by granulation tissue and there appeared to have been a small abscess here. The mucous membrane of the ilium and cæcum was normal. Histological examination showed that chronic inflammatory changes were present in the proximal part of the appendix, but that the walls of its distal part were to a large extent replaced by very vascular granulation tissue, with many polymorphs and occasional foreign body giant cells. Granulation tissue was present in large amounts in the peri-appendicular region and was also found between the coats of the adjoining part of the cæcum, particularly in the submucous layer.

Case 7.—Mrs. E. A., aged 81, admitted May 6, 1954. Abdominal pain had been present for two days, diffuse at first and later settling in the right lower quadrant. There

had been some nausea but no vomiting, and her bowels, previously regular, had not been opened for three days. There was no history of previous abdominal disorder. The temperature was 101° F. and the tongue was furred. In the upper and outer part of the right lower abdominal quadrant, immediately above the anterior superior iliac spine, there was an ill-defined, fixed, tender mass measuring about 1½ in. (4·0 cm.) in diameter, with some guarding of the overlying muscles. Rectal examination was negative. Nothing abnormal was found in the heart and lungs, and the blood-pressure was 180/90. Radiographs of the chest and abdomen showed no abnormality. The hæmoglobin was 10·8 g. per 100 c.c. (73 per cent) and the white blood-count 8600 per c.mm. (polymorphs 85 per cent, lymphocytes 10 per cent, and monocytes 5 per cent). The urine contained nothing abnormal and was sterile on culture.

A diagnosis of appendicular abscess was made and treatment with antibiotics was begun, 800,000 units of penicillin being given daily for 3 weeks and 2 g. of streptomycin daily for 5 days. The temperature remained at approximately 101° F. for 3 days after which it fell, but was elevated again to 100° F. from the tenth to the thirteenth day of the illness. Pain and tenderness were soon relieved, but three weeks after admission the mass remained otherwise unchanged. A barium meal showed a filling defect of the ascending colon just above the cæcum with preservation of the normal mucosal pattern (*Fig.* 48), and this finding was confirmed by barium enema. Tests of the stools for occult blood at this time were consistently positive.

It was thought that the condition was more likely to be inflammatory than neoplastic and that a conservative attitude was justified in a patient aged over 80. Two months after it was first felt the mass was still present and the radiological appearances were unchanged, but occult blood was absent from the stools. At four months the swelling felt distinctly smaller and at five months it was no longer palpable. The patient remained well for the following eight months and there was no recurrence of the swelling in the right iliac fossa. After this she moved to another district.

DISCUSSION

When interval appendicectomy is performed about three months after the occurrence of an appendicular abscess there is usually little trace of the intense inflammation so recently present. The appendix is firmer than normal and for part of its length may be converted into a thin, fibrous cord; if it is retrocæcal in position it may be rather adherent to the cæcum and ascending colon, but it can always be separated from them without much difficulty. There are usually a few peritoneal adhesions, and apart from any distortion resulting from these the ileum and cæcum are unaffected.

In 6 of the present 7 cases a right hemicolectomy was carried out in the belief that the ileocæcal mass was a carcinoma of the cæcum. In each of the resected specimens the appendix was either firmly incorporated in, or largely replaced by, a mass of fibrous and granulation tissue, which penetrated between all the coats of the adjacent part of the cæcum or of the terminal ileum. In those cases in which the affected part of the appendix was not obliterated, its wall was much thickened by chronic inflammatory changes and its mucous membrane was almost completely destroyed, but in the whole series there was never more than very limited involvement of the mucous membrane of the cæcum. So adherent was the appendix that, even if the true diagnosis had been made at operation, removal of the appendix alone would have been impossible without severely damaging the ileum or cæcum. In *Case* 1, the only one in which the terminal ileum was involved, contraction of the fibrous tissue caused an ileal stricture and intestinal obstruction.

A comparatively small number of cases of this type has been recorded, and the condition has been given a variety of names including "fibroplastic appendicitis" (Läwen, 1914), "ligneous cæcitis" (Wilson, Dockerty, Waugh, and Bargen, 1949), and "pseudoneoplastic appendicitis" (Plotegher, 1952). The term 'appendicular granuloma' is suggested because it indicates the origin of the disease, its pathological nature, and the formation of a mass. A satisfactory explanation for the occurrence of this unusual type of appendicitis has not previously been put forward.

Pathology.—Careful examination of the specimens has failed to show any evidence of the known specific inflammatory processes which occur in the ileocæcal region or elsewhere, so it must be presumed that appendicular granuloma is the result of an unusual development of the ordinary form of acute appendicitis. Three factors appear important in the production of this uncommon condition: the position of the appendix, rupture of an appendicular abscess into the cæcum, and the age of the patient.

Position of the Appendix.—In addition to the large amount of granulation and fibrous tissue produced in these cases, a striking feature is the manner in which this tissue extends into and between the coats of the cæcum and ileum, incorporating them into one mass with the appendix. This suggests a particularly close initial relationship of the appendix to the ileum or cæcum. In 5 of the 6 cases in which resection was carried out the appendix was retrocæcal in position, and in one (*Case* 1) it lay behind the ileocæcal junction and terminal ileum. The appendix was retrocæcal in most of the cases previously described, and it has been said that inflammation is more easily sealed off here and that this favours the formation of a granuloma. It was shown by Wakeley (1933), however, that the retrocæcal position is the commonest in which the appendix is found, so this position cannot be held to explain so simply such an unusual condition. Moreover, it is no uncommon event for an acutely inflamed retrocæcal appendix to perforate into the general peritoneal cavity.

The retrocæcal appendix usually lies in the right paracolic gutter where it may be intraperitoneal, having a mesentery, or extraperitoneal, lying immediately beneath the peritoneal reflection from the ascending colon to the posterior abdominal wall (*Fig.* 49). An appendix in either of these sites is clearly visible in the normal state on opening the abdomen, and if it were to be the origin of an appendicular granuloma it would be expected that some part of the appendix would always be recognizable at operation. On the contrary, in none of the cases in this series was any part of the appendix distinguishable until the cæcum had been mobilized from the posterior abdominal wall.

Much less commonly the retrocæcal appendix lies directly behind the cæcum and ascending colon. There may then be a deep retrocæcal and retrocolic pouch of peritoneum, to which the appendix has

a variable relationship; or the posterior aspect of the cæcum may be entirely devoid of a peritoneal covering, when the appendix lies between the cæcum and posterior abdominal wall, having no contact with the peritoneum whatever (*Quain's Elements of Anatomy*, 1914). It is probably the last type of retrocæcal appendix (*Fig.* 50), largely buried out of sight even in the normal state and having little or no relationship with the peritoneum, which is responsible for the type of case described here.

Rupture of an Appendicular Abscess into the Cæcum.—If the appendix is buried behind the ascending colon and is not in contact with the

FIG. 49.

FIG. 50.

FIG. 49.—Extraperitoneal retrocæcal appendix lying immediately beneath peritoneum in right paracolic gutter.

FIG. 50.—Retrocæcal appendix lying directly behind cæcum and not related to peritoneum.

peritoneum there is a much greater chance of the infection remaining localized even though perforation occurs, but some explanation is still required as to why the inflammatory process penetrates between the various layers of the wall of the adjacent bowel.

Rupture of an appendicular abscess externally, into the general peritoneal cavity, or into the rectum can be recognized clinically without difficulty. Most text-books mention the cæcum as another situation for rupture of such an abscess, but it is very doubtful how often this actually occurs because it is not an event associated with any particular combination of symptoms and signs. There is some evidence, however, that it occurred in three of the cases in the series described here: in *Case* 2 (*Fig.* 44) a narrow, fistulous track led directly backwards from the cæcum into a small appendicular abscess cavity; in *Case* 3 the granulomatous mass incorporating the appendix had ulcerated into the cæcum over a small area, suggesting that an abscess had ruptured here and that resolution was occurring; and in *Case* 7, in which no operation was performed, occult blood was consistently present in the stools in the early stages of the illness, but later disappeared. The findings in *Cases* 3 and 7 may have another explanation, but it is remarkable that of 5 similar cases described by Musgrove and Dockerty (1950) 3 had a fistula between the abscess and the cæcum and 1 had a similar communication with the ileum.

Rupture of an appendicular abscess into the rectum is usually followed by rapid healing, but conditions in the cæcum are different from those in the rectum and subsequent progress may be correspondingly modified if the abscess bursts here. The rectum is usually empty. The fæces passing through it are of a soft, solid consistency, and although said to consist of one-quarter to one-third by weight of bacteria, most of these are dead. The cæcum is rarely empty. Its contents are fluid, and little precise information is available as to the number of bacteria present under normal circumstances, but there is no reason to believe there are less live bacteria in the cæcum than in the rectum and there are probably many more.

The intra-luminal pressure of the cæcum is another matter about which little is known. When the progress of a barium meal is watched on a fluorescent screen little or no movement of the cæcum and ascending colon is seen. It appears that in the upright position the onward movement of the intestinal contents in this part of the bowel is the result of more and more fluid passing through the ileocæcal valve and the excess overflowing into the transverse colon (Barclay, 1936). This means that in the sitting or standing position considerable hydrostatic pressure will be present in the cæcum. During defæcation the pressure in the cæcum will become very much higher as a result of voluntary contractions of the abdominal muscles, although it will not be as high as the pressure in the rectum, which is further increased as a result of mass peristalsis in the colon. If an abscess has recently perforated into the cæcum there is thus considerable inducement for the infected fluid cæcal contents to be driven into the abscess cavity. Any pressure applied to the cæcum from without is, of course, equally applied to a communicating abscess, but if, as was certainly the case in the patients of this series, the cavity has firm thick walls, the rise of pressure in the abscess cavity will be less than that in the cæcum and the cæcal contents will tend to flow into the abscess.

A further way in which rupture of an appendicular abscess into the cæcum differs in its effect from rupture into the rectum is that in the latter case dependent drainage is more likely to result than in the former.

At least three factors, relating to the bacterial content of the bowel, intra-luminal pressure, and efficiency of drainage, tend to delay resolution after rupture of an appendicular abscess into the cæcum. *It is suggested that the additional time during which active inflammatory changes may continue accounts for the excessive amount of granulation tissue produced and for the subsequent fibrosis, and that the breach in the wall of the cæcum provides an entry through which the infection can gain access to the connective tissue spaces between its layers, causing the thickening of the bowel wall and the extreme adherence of the appendix to the cæcum, which are characteristic of appendicular granuloma.*

Age.—The age incidence of appendicular granuloma contrasts sharply with that of the ordinary form of acute appendicitis, which is much commoner before 40 years than after it (Aird, 1957). Five of the seven patients in the present series were over 70 years of age and the other two were between 50 and 60. Other authors have found a similar age distribution and have been unable to account for it adequately

If it is correct that appendicular granuloma is the result of a 'buried' retrocæcal appendix becoming acutely inflamed and rupturing into the cæcum, and that this is a rare event in appendicitis generally, it would be expected that some change normally found in the appendix with advancing years would account for its rupture into the cæcum. The most obvious of these changes is in the lymphoid tissue, which diminishes in amount after the age of 30 and is practically absent after 70 (Berry and Lack, 1906). In addition the tubular glands of the mucosa diminish in number and atrophy as age advances. Wilson and others (1949) suggest that a diminished secretory power of the mucosa of the appendix in the elderly causes slower distension in acute obstructive appendicitis and allows time for adhesions to consolidate before rupture occurs. Musgrove and Dockerty (1950) believe that obstruction of the appendix and consequent rupture are delayed because of the smaller amount of lymphoid tissue present in old people.

Neither of these theories takes into account that in young people with acute appendicitis gangrene and perforation may never occur, and that if the appendix does perforate it may do so within forty-eight hours of the onset or only after several days, while in a high proportion of elderly patients the acutely inflamed appendix has become gangrenous by the second day of the illness and that, if not removed by operation, all or most of it often sloughs away completely. These features of acute appendicitis in old people are attributed by Taylor (1935) to sclerosis of the appendicular vessels which are unable to deliver the increased blood-supply required by the inflammatory process.

It appears reasonable to suppose that in an elderly person, when the appendix is in the buried retrocæcal position, firmly wedged between the posterior abdominal wall and the cæcum or ascending colon, the rapid spread of inflammation, with early and widespread gangrene of the appendix, may also cause necrosis of the adjacent cæcal wall before a large abscess can form, whereas in a younger person the slower progress of the disease does not cause the same damage to the cæcum, the wall of which remains intact. In support of this view is the fact that in cases of appendicular granuloma there is frequently little trace of that part of the appendix within the inflammatory mass, confirming that a large part of the organ has sloughed.

Both the naked-eye and histological changes of appendicular granuloma are in some respects similar to those occurring in diverticulitis of the pelvic colon. The question as to whether any of this group of cases could have been due to cæcal diverticulitis has been carefully considered, but in each case there is convincing proof that the disease began in the appendix and in none has there been any evidence of a cæcal diverticulum.

There is some doubt as to whether an appendicular granuloma will resolve completely if it is not removed. Information about this is likely to be extremely difficult to obtain because in cases in which resection is not performed there will always be some uncertainty about the diagnosis. In this respect it is probably unsafe to diagnose appendicular granuloma unless the patient is over 50 and the mass disappears after being palpable for at least two months. In *Case* 7 the diagnosis appeared reasonably certain and complete recovery occurred in five months, but in three of the cases described by Musgrove and Dockerty surgery was required four years, eighteen months, and five months respectively after the onset of symptoms. It is perhaps significant that *Case* 7 was given a prolonged course of antibiotics. The exact position of the appendix may to some extent determine the result. If it lies behind the terminal ileum or ileocæcal junction fibrosis may occlude the ileum and cause intestinal obstruction, as occurred in *Case* 1. If the appendix is related only to the cæcum or ascending colon, the wider lumen in this part of the bowel may allow the inevitable contraction of scar tissue without subsequent obstruction.

Clinical Features.—All the cases of appendicular granuloma described in this paper had pain in the right iliac fossa, except one which had the central abdominal colic of intestinal obstruction (*Case* 1); in 4 the onset was acute and symptoms had been present for periods varying from 2 days to 2 weeks; in the other 3 cases the onset was gradual and the pain had been present for 2, 4, and 12 months respectively. In 5 cases there was no vomiting and no significant change of bowel habit; 2 had vomiting and diarrhœa. In only 2 cases (*Cases* 5 and 7) was there a rise of temperature to over 100° F., and only 1 patient (*Case* 1) had lost weight. In 5 cases there was a hard, fixed, and tender mass in the right lower abdominal quadrant; in *Case* 5 the mass was in the right upper quadrant, and in *Case* 1 it was only palpable per rectum.

In only 1 patient was the hæmoglobin below 85 per cent (*Case* 7). In this patient the stools were strongly positive to tests for occult blood at first, but later became negative. Tests for occult blood were carried out in 3 other patients, the results being negative in 1 and variable in 2. White blood-counts were not remarkable. Of the 4 cases with an acute onset and a short history, one had chronic lymphatic leukæmia; the other 3 had a mild polymorphonuclear leucocytosis, the highest count being in *Case* 6, in which there were 9600 leucocytes per c.mm. with 84 per cent polymorphs. There was no leucocytosis in the cases in which the onset was gradual.

Radiological Appearances.—A localized inflammatory mass on the posterior aspect of the cæcum or ascending colon, with at most very limited mucosal changes such as a fistula or small ulcer, may show no abnormality on barium-meal or enema examination, as in *Cases* 3 and 5. A filling defect is most likely to be seen on a barium meal follow-through or on the post-evacuation films of a barium enema, and over it there may be normal mucosal folds as in *Cases* 2 and 7. This filling defect may easily be obscured if the cæcum is distended with the opaque medium. An additional reason for having a barium meal if possible as well as an enema is that an enema alone will often give an erroneous impression of the site of the ileocæcal valve if there is a pathological lesion in this region.

Diagnosis.—Nearly all the recorded cases of appendicular granuloma have been operated upon because they were thought to have carcinoma of the cæcum or ascending colon, or because carcinoma

could not be excluded on clinical grounds. In attempting to distinguish between the two conditions symptoms and signs are of little help. Local pain and a tender mass occur frequently with carcinoma in this region, resulting from infection in and around the growth, distension of the cæcum or of the appendix, or even actual appendicitis; the history may be short, and while investigations are being carried out the mass may diminish in size. Loss of weight may be significant; it was found by Muir (1956) in 50 per cent of 109 cases of carcinoma of the right colon, but it is unusual in appendicular granuloma.

More assistance may be obtained from the special investigations. Anæmia is extremely common in carcinoma of the cæcum and the stools are usually strongly positive to tests for occult blood. The hæmoglobin was below 10·4 g. per 100 c.c. (70 per cent) in 23·8 per cent of Muir's cases, and of 140 cases of right colon carcinoma analysed by Person and O'Neill (1950) the hæmoglobin averaged 10·9 g. per 100 c.c. (74 per cent) and occult blood was present in the stools in 80 per cent. The radiological appearance of a cæcal carcinoma may be quite different from that of an appendicular granuloma, as all or most of the surface of a carcinoma is ulcerated and no mucosal pattern is visible in relation to the filling defect, but it is unusual for the mucosal folds over an extra-cæcal mass to be seen clearly enough for much importance to be attached to this point. Demonstration of a significant length of the appendix would be strong evidence against the lesion being of appendicular origin.

Treatment.—Owing to the difficulty of excluding carcinoma, and the doubt whether an appendicular granuloma will resolve spontaneously, it is inevitable that most cases will be operated upon. In any group of elderly patients, however, a proportion will be unfit for major operative procedures because of cardiovascular or respiratory disease, obesity, or old age. If appendicular granuloma is suspected in such a case and there is no strong evidence of carcinoma a comparatively long period of observation, with antibiotic treatment, may be justified. The relative dangers of waiting and of operation must be a matter for assessment in each individual case.

When an appendicular granuloma is exposed at operation the typical finding is a hard mass situated in the posterior wall of the cæcum and fixed to the posterior abdominal wall. Usually the appendix cannot be recognized at all until the cæcum has been mobilized, after which its proximal part may be seen and when followed becomes lost in the retrocæcal mass. Carcinoma of the cæcum frequently obstructs the appendix and is sometimes complicated by acute appendicitis, but it is very unusual for the appendix to be engulfed by the growth. If the appendix is buried in the mass the latter is therefore likely to be inflammatory in nature and appendicular in origin.

It will be appreciated from the description already given of the pathology of appendicular granuloma, and from *Figs.* 41 and 46, that simple appendicectomy is not possible, because even if sufficient of the appendix remains to be identified it is so firmly fused to the posterior wall of the cæcum or ileum that the two structures cannot be separated. If there is a plane of cleavage between the cæcum and the whole length of the appendix the condition is not an appendicular granuloma in the sense used here. Inflammatory changes confined to the appendix may have resulted in thickening and induration of its wall, but are unlikely alone to be the cause of a persistently palpable mass and there is probably a separate lesion in the cæcum, such as a small carcinoma, obstructing the orifice of the appendix.

Because of these difficulties a right hemicolectomy is probably the best procedure when an appendicular granuloma is first recognized at laparotomy. If the general condition of the patient is giving rise to anxiety a local resection of the appendix and the adjacent cæcal wall is a possible alternative, beginning the procedure by opening the cæcum anteriorly in order to inspect the mucosal aspect of the mass and exclude carcinoma.

SUMMARY

Seven cases of appendicular granuloma have been described.

Their unusual pathological features are due to rupture of an appendicular abscess into the cæcum.

Clinically they have a very close resemblance to carcinoma of the cæcum.

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REFERENCES

AIRD, I. (1957), *A Companion in Surgical Studies*, 2nd ed., p. 852. Edinburgh and London: E. & S. Livingstone.

BARCLAY, A. E. (1936), *The Digestive Tract*, 2nd ed., p. 170. London: Cambridge University Press.

BERRY, R. J. A., and LACK, L. A. H. (1906), *J. Anat., Lond.*, **40**, 247.

LÄWEN, A. (1914), *Dtsch. Z. Chir.*, **129**, 221.

MUIR, E. G. (1956), *Brit. J. Surg.*, **44**, 1.

MUSGROVE, J. E., and DOCKERTY, M. B. (1950), *Arch. Path. (Lab. Med.)*, **50**, 427.

PERSON, E. C., and O'NEILL, E. A. (1950), *Int. Abstr. Surg.*, **90**, 320.

PLOTEGHER, A. (1952), *Arch. ital. Mal. Appar. dig.*, **18**, 348.

Quain's Elements of Anatomy, Ed. SCHAFER, SYMINGTON, and BRYCE (1914), 11th ed., p. 113. London: Longmans, Green.

TAYLOR, H. (1935), *Lancet*, **2**, 937.

WAKELEY, C. P. G. (1933), *J. Anat., Lond.*, **67**, 276.

WILSON, J. W., DOCKERTY, M. B., WAUGH, J. M., and BARGEN, J. A. (1949), *Arch. Surg., Chicago*, **59**, 933.

SOME ASPECTS OF ADENOCARCINOMA OF THE APPENDIX

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CARCINOMA of the appendix was first reported in 1882 by Beger. Since then several cases with reviews of the literature have been reported. Uihlein and McDonald in 1943 were the first to produce a simple classification when they described a carcinoid type (88·2 per cent), a cystic type (8·3 per cent), and a colonic type (3·5 per cent). The carcinoid tumour is well recognized and will not be discussed in this paper. The cystic type is described as leading to pseudomyxoma peritonei; Willis (1948), however, does not recognize the occurrence of a cystic type and thinks the histological picture is due to pressure distortion in a mucocele of the appendix and to an increase in the number of goblet cells. No examples of the so-called malignant mucoceles have been encountered in this series. The colonic type is both macroscopically and microscopically similar to an adenocarcinoma of the colon.

Four of the cases reported in this paper have been treated at the Middlesex Hospital and the other (*Case* 4) at St. Bartholomew's Hospital. The four Middlesex Hospital cases were all that could be traced in this hospital between 1926 and 1956. During this same period 29 carcinoid tumours of the appendix were examined in the pathology department of the hospital. During the same time 4838 appendicectomy specimens were examined histologically, of which 1424 showed acute inflammatory changes; the remainder were normal or showed chronic appendicitis. The incidence of acutely inflamed appendices with an underlying carcinoma was 2 in 1424, or 0·14 per cent. This figure does not represent a true occurrence rate as many appendices that are obviously acutely inflamed never reach the pathological department; on the other hand, it is quite possible that a malignant appendix could have been similarly discarded.

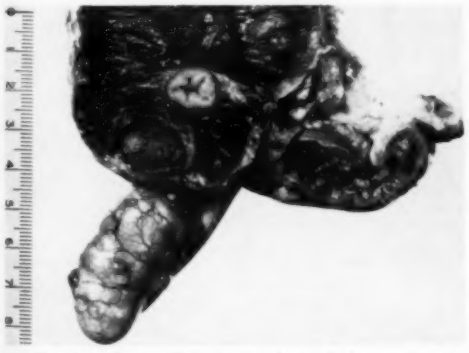

FIG. 52.—*Case* 2. Operation specimen of adenocarcinoma of the appendix. The tumour can be seen in the orifice of the appendix. The scale is in centimetres.

In this paper 5 cases of the colonic type of tumour will be described. The question of clinical and pathological diagnosis will be discussed; the importance of routine histological examination of excised appendices will be stressed, the method of treatment outlined, and the prognosis briefly discussed.

CASE REPORTS

Case 1.—M. S., female, aged 67. She was admitted as an emergency on April 19, 1926, complaining of severe epigastric pain for five days; she had not been feeling well for the previous two days. On examination her temperature was 99·4° F., pulse-rate 100/min., and respiration rate 24/min. Her breath was foul and she looked ill; there was no rigidity of the abdominal muscles, but a

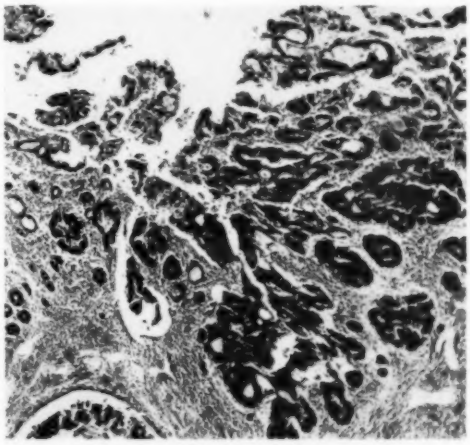

FIG. 51.—*Case* 1. Adenocarcinoma of the appendix invading the submucosa. H. and E. (× 40.)

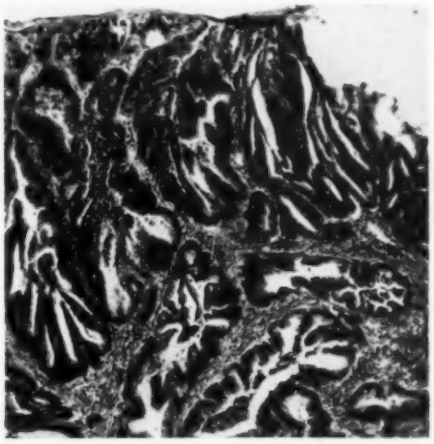

FIG. 53.—*Case* 2. Low-grade adenocarcinoma invading the muscular coat of the appendix. H. and E. (× 50.)

swelling was palpable in the right iliac fossa—the long axis extending downwards. On April 21 a laparotomy by Mr. A. E. Webb-Johnson revealed a large amount of free pus in the peritoneal cavity, and a mass, the size of a walnut, around a perforated appendix, was adherent

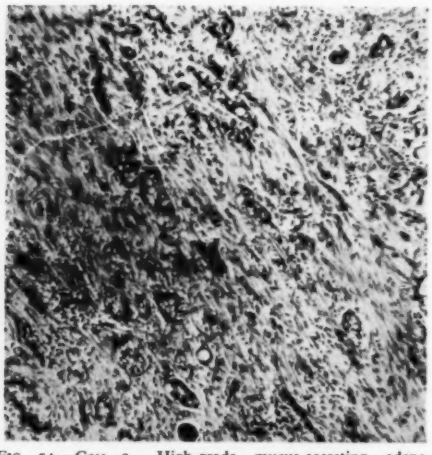

FIG. 54.—*Case* 3. High-grade mucus-secreting adenocarcinoma of appendix invading muscle. H. and E. (× 65.)

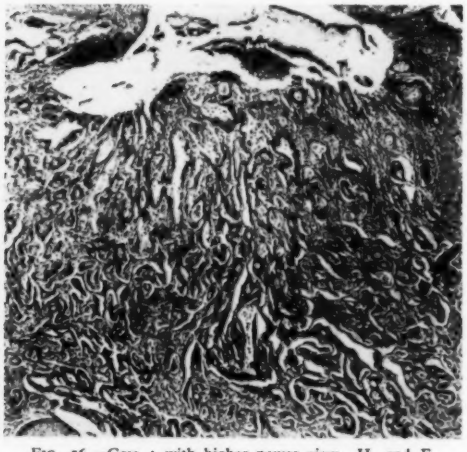

FIG. 56.—*Case* 4 with higher power view. H. and E. (× 60.)

to the cæcum and the ileum. The appendicular mass was excised and holes in the cæcum and ileum repaired. Drainage tubes were then inserted into the ileum and peritoneal cavity and the abdomen was closed. After operation the patient went rapidly downhill and died on April 25. A limited post-mortem examination showed that she died of general peritonitis and that there were no secondary deposits.

On microscopy the excised tumour was seen to be a columnar-cell carcinoma of the appendix invading a fibrous stroma and organizing granulation tissue (*Fig.* 51).

Case 2.—A. J., female, aged 51. First seen in 1949 when she complained of feeling generally unwell. On examination a mass was palpable in the right iliac fossa. An exploratory operation was advised, but permission was refused. Two years later she again sought advice as she was no better. On examination the mass was still present and on this occasion she agreed to operation. At

FIG. 55.—*Case* 4. Low-power view showing deep invasion of appendix tissues by adenocarcinoma. H. and E. (× 14.)

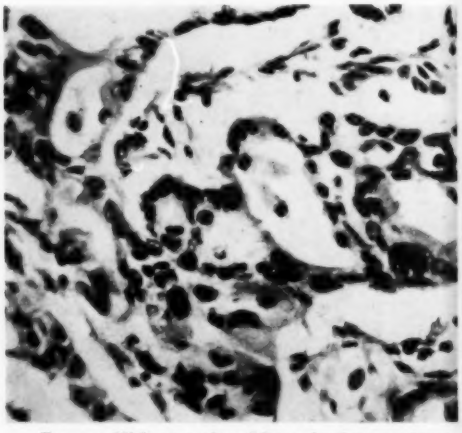

FIG. 57.—High-power view of *Case* 4 showing some degree of tubule formation but irregular and mitotic cells. H. and E. (× 360.)

laparotomy by Mr. C. J. B. Murray in July, 1951, a mucocele of the appendix with a tumour at its base was found; there was no evidence of metastases in the liver or other abdominal organs and a right hemicolectomy was performed. The specimen consisted of 4 in. of cæcum, 2 in. of terminal ileum, and a distended appendix 2 in. long. On opening the specimen a polypoid growth ½ in. in diameter was seen to be obstructing the orifice of the appendix and causing a mucocele of the appendix (*Fig.* 52.) Histologically the tumour was an adenocarcinoma of low-grade malignancy which invaded, yet was confined to, the bowel wall (*Fig.* 53). Five lymphatic glands in the mesentery were examined, but none were invaded by growth. The patient is alive and well five and a half years later.

Case 3.—R. S., male, aged 51. Admitted as an emergency on Aug. 30, 1954, with a forty-eight-hour history of abdominal pain localizing to the right iliac fossa, and preceded for twenty-four hours by nausea and constipation. On examination his temperature was 99·6° F., pulse-rate 85/min.; respiration rate 20/min. He looked ill and his tongue was furred; guarding and rebound tenderness were detected in the right iliac fossa. An acutely inflamed appendix which had perforated at its tip was removed through a grid-iron incision on the same day. There was free pus in the peritoneal cavity. Microscopy of the appendix showed invasion of all coats of an acutely inflamed appendix by a mucus-secreting adenocarcinoma, the appearance of which was suggestive of appendicular origin rather than a secondary deposit, though this could not be excluded (*Fig.* 54). A barium meal and follow-through showed no lesion, and nine weeks after the appendicectomy Mr. C. J. B. Murray performed a formal right hemicolectomy. No tumour could be found elsewhere in the abdomen at this operation. External examination of the specimen showed an area of thickening 1 in. in diameter at the site of the base of the appendix. On opening the specimen the bowel wall appeared to be invaded by tumour, but the mucosa overlying the base of the appendix was intact. Histologically the appearance of the growth was similar to that of the appendix and the tumour had spread through the bowel wall to involve the peritoneal surface; ten lymph-glands from the mesentery were examined and all were free of tumour. The patient is alive and well three and a half years later.

Case 4.—J. B. N., male, aged 43. First seen in March, 1955, with a three-months' history of recurrent attacks of right-sided abdominal pain. Ten years previously he had had amœbic hepatitis. On examination a tender mass in the right iliac fossa was palpable. The white blood-count was 17,000/c.mm. (80 per cent polymorphs). A diagnosis of an appendix mass was made and bed-rest was advised. The mass resolved during the next three weeks but he had two further attacks of pain during the next twelve weeks. In the last attack there was tenderness in the right iliac fossa and because of the rising pulse-rate, operation was considered advisable. On July 7 Mr. Philip Shemilt operated and removed a very adherent thickened appendix; two pinpoint white specks on the mesentery of the terminal ileum were noticed at the time; no enlarged glands were seen along the main vessels. Appendicectomy was uneventful, although the base of the appendix was friable. Post-operatively there was slight abdominal distension but this settled on conservative treatment. Histology showed a carcinoma of the appendix of average grade malignancy extending to the serosa (*Figs.* 55–57). The patient was seen by Mr. C. Naunton Morgan, who advised laparotomy, and on Aug. 2 the abdomen was explored through a right-sided paramedian incision. Multiple peritoneal deposits were seen and a frozen section of one of the nodules confirmed the diagnosis of carcinoma. The primary mass was about ¾ in. in diameter at the site of the appendix stump. Both the small and large intestines were distended and an ileo-transversostomy was performed. Post-operatively the patient's condition gradually deteriorated and he died on Oct. 2. No post-mortem examination was performed.

Case 5.—M. M. G., female, aged 43. In December, 1955, she complained of central abdominal pain for the previous nine months. Previously, she had had an appendicectomy at the age of 15, but no pathological report on the specimen is available. In March, 1955, the appendix scar became inflamed and discharged a little pus. On examination there was a tender mobile lump 1½ in. in diameter in the right iliac fossa. A barium enema showed a rounded filling defect at the cæcal apex, with early distortion of the mucosal pattern. On Jan. 11, 1956, a right hemicolectomy was performed by Mr. C. J. B. Murray; no metastases were seen in the liver or elsewhere. Histology showed that there was invasion of the cæcal wall at the site of the appendix scar by an adenocarcinoma of low-grade malignancy (*Fig.* 58).

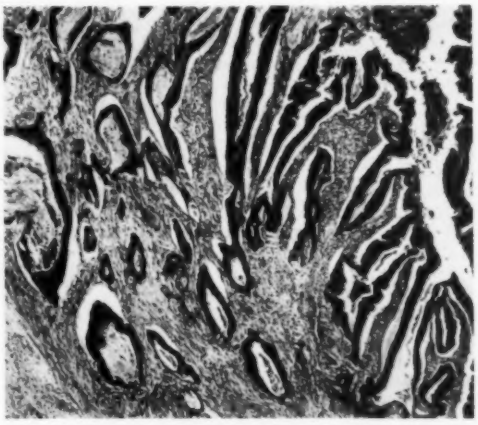

FIG. 58.—*Case* 5. Low-power view of an invading low-grade adenocarcinoma of the appendix. H. and E. (× 45.)

Fifteen glands from the mesentery were examined and all were free of tumour.

DISCUSSION

Various points arising from these cases will be discussed as follows:—

1. The establishment of a correct clinical diagnosis.
2. The pathological diagnosis.
3. The importance of routine histology.
4. The treatment.
5. The prognosis.

1. Clinical Diagnosis.—Three cases (*Cases* 1, 3, and 4) presented as 'acute appendicitis'; in all three no underlying malignant disease was suspected before operation; in *Case* 1 laparotomy revealed a mass which was possibly malignant; the other two cases at operation appeared to be uncomplicated examples of acute appendicitis. The two white specks on the mesentery in *Case* 4 were at that time not thought to be of any significance. Schuldt (1940) mentions that the diagnosis can sometimes be suspected at operation. Sieracki and Tesluck (1956), in a paper which gives an admirable review of the literature, stress that the diagnosis is not usually made pre-operatively, and that two-thirds of the cases present as an acute appendicitis.

In the other two cases (*Cases* 2 and 5) a mass was palpable and a malignant tumour, most probably arising in the cæcum, was suspected before operation. In *Case* 2 involvement of the appendix was not suspected until the abdomen was opened; in *Case* 5 the filling defect in the lower pole of the cæcum on the barium enema raised the possibility of a tumour arising in or near the base of the appendix.

2. Pathological Diagnosis.—The correct pathological diagnosis is also not always easy to establish. In the three acute cases (*Cases* 1, 3, and 4) the diagnosis was made on histological grounds; when an adenocarcinoma is seen to be invading the

appendix the possibility that it may be a secondary from elsewhere, especially higher up the alimentary tract, should be borne in mind. Unfortunately, the post-mortem report on the first case says no more than that the patient died of peritonitis; no mention is made of the other intestinal organs. However, the carcinoma, as in the other two acute cases, arose from the mucosa of the appendix. In *Case* 3 the possibility that the tumour might have been a metastasis from higher in the alimentary tract was excluded by radiography; in *Case* 4 the surgeon at the first operation did not see any widespread evidence of new growth and it was therefore assumed that the growth was arising primarily in the appendix. In the other two cases (*Cases* 2 and 5) the diagnosis was apparent on the macroscopical appearances. In *Case* 2 a protuberant growth could be seen to be emerging from the orifice of the appendix. The growth in *Case* 5 had a similar protuberant appearance, but it was only because the tumour was arising in the mucosa overlying the appendix scar that a diagnosis of carcinoma arising in the appendix stump was made. These two tumours are very similar to the common type of polypoid carcinoma of the cæcum and could easily be diagnosed as such unless care was taken to notice the exact site of origin.

It is also important to distinguish histologically between an adenocarcinoma and a carcinoid tumour of the appendix. It is now thought that some of the earlier recorded cases of adenocarcinoma were in fact carcinoid tumours (Sillery, 1951). In this present series, two cases which had been classified as carcinoma of the appendix have been omitted, as the histological picture was more that of a carcinoid than of an adenocarcinoma.

3. Routine Histology.—It cannot be stressed too strongly that routine histology should be performed on all appendix specimens. It is almost impossible on clinical grounds to suspect that there is an underlying carcinoma in a case of acute appendicitis. Although carcinoma of the appendix is very rarely encountered it is suggested that some cases have remained undiagnosed as the pathologist has never had an opportunity to discover their presence. Likewise, at a necropsy on a patient dying from carcinomatosis the appendix or appendix stump, when the appendix has been removed, should be carefully inspected as a possible source of the carcinomatosis.

4. Treatment.—From the clinical viewpoint the treatment of carcinoma of the appendix depends upon whether malignant disease has been suspected before operation or not. In the two non-acute cases a right hemicolectomy was the obvious choice of treatment; this was done after the bowel had been suitably prepared for a resection and anastomosis.

In the acute cases the problem is more difficult; in *Case* 3, on learning that a carcinoma was present, it was impossible to be certain that all the tumour had been removed. Hence a hemicolectomy was performed and residual tumour was found in the remains of the appendix stump. Likewise in *Case* 4 a laparotomy was performed five weeks after appendicectomy, but unfortunately there were many peritoneal metastases present. No reports have been found of carcinoma of the appendix being successfully treated by radiotherapy. Thus the suggested treatment is that a right hemicolectomy should be done as soon as the correct diagnosis has been established.

5. Prognosis.—The prognosis of these tumours depends upon both the extent of spread of the tumour and the individual degree of malignancy; these must be correlated to enable an attempt at prognosis to be given. Schuldt (1940) states that if rupture of the appendix occurs then metastases will be present within a year. Sieracki and Tesluck (1956) state that a growth invading the submucosa of the appendix will reach the peritoneum quicker than in the cæcum, owing to a deficiency of the muscle coat in the appendix; they maintain that a growth reaching the submucosa of the appendix is automatically subperitoneal. Case 3 is still alive and well after three and a half years, in spite of having a high-grade tumour in a perforated appendix. *Case* 2 has now survived over five years, as would be expected from the pathological picture.

SUMMARY

Five new cases of adenocarcinoma of the appendix are reported. Adenocarcinoma of the appendix must be carefully differentiated from carcinoma of the cæcum and histologically from a carcinoid tumour. In a proportion, some cases present as acute appendicitis; in these only microscopy will reveal the presence of carcinoma. Right hemicolectomy, it is suggested, is the correct treatment, even if this has to be done as a second operation after routine histological examination of the appendix. The prognosis in adenocarcinoma of the appendix associated with acute appendicitis seems to be relatively poor owing to the difficulties in early diagnosis and the ease with which the tumour can reach the peritoneum. On the other hand, when no overlying acute inflammatory lesion is present, the prognosis is much better.

My thanks are due to Lord Webb-Johnson, Mr. C. Naunton Morgan, Mr. C. J. B. Murray, and Mr. P. Shemilt for permission to quote their cases; to Dr. P. S. Andrews for his advice and assistance with the photomicrographs; to Lt. Colonel D. W. Bell, R.A.M.C., for the loan of the slide to obtain *Figs.* 55, 56, and 57 and to Mr. M. Turney for *Fig.* 52.

REFERENCES

BEGER, A. (1882), *Berl. klin. Wschr.*, **19**, 616.
SCHULDT, F. C. (1940), *Minn. Med.*, **23**, 791.
SIERACKI, J. C., and TESLUCK, H. (1956), *Cancer*, **9**, 997.
SILLERY, R. J. (1951), *J. Amer. med. Ass.*, **147**, 854.
UIHLEIN, A., and MCDONALD, J. R. (1943), *Surg. Gynec. Obstet.*, **76**, 711.
WILLIS, R. A. (1948), *Pathology of Tumours*, 426. London: Butterworth.

ACUTE NECROTIZING (PSEUDOMEMBRANOUS) ENTEROCOLITIS

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Acute necrotizing (pseudomembranous) enterocolitis has been recognized by pathologists for more than fifty years, but only recently has it aroused the interest of clinicians. Since the review of Penner and Bernheim (1939) a number of authors in America (Dixon and Weismann, 1948; Prohaska, Govostis, and Tabenhaus, 1954; Weismann and Twitchell, 1956) and in this country (Bruce, 1955; Dawson-Edwards and Morrissey, 1955) have emphasized the importance of this condition as a post-operative complication, especially after abdominal surgery. Because of this, the clinical labels commonly applied are 'acute post-operative enterocolitis' and 'post-operative necrosis of the intestinal mucous membrane'. Other observers, however, have indicated that this pathological entity may also occur in association with a variety of non-surgical conditions, of which heart disease is the commonest (Kleckner, Bargen, and Baggenstoss, 1952).

Since the introduction of the broad-spectrum antibiotics, many cases of enteritis attributed to infection by resistant strains of staphylococci have been recorded. Some of these have been characterized by necrosis of the intestinal mucous membrane, but the assumption that staphylococcal enteritis and acute necrotizing enterocolitis are variants of the same condition is by no means certain. Until recently there has been a paucity of adequate bacteriological studies, but in a number of cases of necrotizing enterocolitis it has now been shown that staphylococci are definitely absent. Furthermore, in many cases of staphylococcal enteritis the inflammatory changes in the bowel are not accompanied by necrosis of the mucous membrane (Dearing, 1956). To distinguish between these two conditions is important, because it appears that staphylococcal enteritis is a potentially reversible disease and is not invariably fatal. The prognosis of necrotizing enterocolitis, on the other hand, is grave, and few recoveries have been reported.

In this paper we have reviewed 16 cases of acute necrotizing enterocolitis which were verified at autopsy, and have considered the aetiology and pathogenesis of the condition. Three illustrative cases of the series are reported in detail, one of them a patient with rheumatic heart disease, and two post-gastrectomy cases.

CASE REPORTS

Case 7.—A male clerk, aged 50, was first admitted to hospital on Jan. 13, 1956, with the following history. Four days previously he had developed sudden severe cramp-like pain in the left leg and a sensation of alternate heat and cold in the limb. The pain passed off in a short time, but he then found that he could not walk more than a few steps without recurrence of the pain and he noted that his left foot became pale. He was admitted with a diagnosis of acute arterial occlusion. The clinical findings supported a diagnosis of acute occlusion of the left popliteal artery. The occlusion was thought to be embolic as he had rheumatic heart disease with dominant mitral regurgitation and auricular fibrillation, the presence of which had been known for eight years, and for at least seven years he had been taking Nativelle's digitalin $\frac{1}{100}$ gr. daily. He was treated with the anticoagulant phenindione, and his progress was uneventful until the twenty-fourth day when he developed a sensitization rash on his forearm. Within 48 hours he had a severe exfoliative dermatitis. This was treated in the first instance with promethazine. Four days later his temperature rose abruptly and he developed signs of a right basal pneumonia. At this time he was seriously ill. He was given tetracycline 500 mg. 4 times a day and this was followed by a dramatic response, both as regards his pyrexia and his general condition. The dosage of tetracycline was reduced to 250 mg. after forty-eight hours and it was discontinued after 5 days. On the third day of tetracycline therapy he developed diarrhœa and passed six rather loose greenish stools. Bacteriological examination of these did not reveal the presence of any intestinal pathogens. After the short course of tetracycline the patient improved steadily. His skin lesions cleared and the signs at the right base resolved. Four days after the tetracycline had been stopped he complained of a feeling of compression in the chest. His blood-pressure fell abruptly and an electrocardiogram showed the changes of an anterolateral myocardial infarction. Because of the known sensitivity to phenindione he was treated with heparin only. For forty-eight hours his condition remained satisfactory, but he then developed severe peripheral circulatory failure with intense cyanosis of the limbs. This did not respond to the administration of noradrenaline in an intravenous drip. He died two days later. Diarrhœa had stopped when the tetracycline was discontinued but during the last forty-eight hours he was incontinent and passed dark green semi-solid fæces.

Morbid Anatomy.—Autopsy was performed 24 hours after death. The skin of the arms and legs showed a distinct greenish coloration which, in the case of the arms, was clearly demarcated from normal skin by a narrow but definite zone of hyperæmia. The stomach contained a little altered blood but the mucosa was normal. In the first part of the duodenum there was a subacute peptic ulcer. The small intestine showed no abnormality other than an occasional admixture of altered blood with the intestinal contents. The large bowel was empty apart from an excessive amount of bile-stained mucus; the mucosa was hyperæmic and œdematous and was studded throughout its whole length with small, slightly elevated, pale yellowish, firmly adherent plaques. These lesions were numerous and often closely set, but seldom confluent. They measured up to 1·0 cm. in diameter (*Fig.* 59).

The heart (440 g.) was the seat of a severe 'button-hole' type of mitral stenosis and there was also an extensive recent myocardial infarct involving the anterior wall of the left ventricle and much of the inter-ventricular septum. The coronary arteries were severely atheromatous and the left coronary artery was occluded by red thrombus. There was a large recent infarct in the right kidney. The liver and spleen showed evidence of chronic venous congestion. The lower end of the left popliteal artery was occluded by adherent red thrombus. In the left lobe of the cerebellum there was an area of old ischæmic softening. Other organs showed no notable abnormality.

Microscopical Findings.—The jejunum and ileum showed no abnormality other than autolytic changes with loss of surface epithelium from the villi. The discrete plaques with which the mucosal surface of the large bowel was studded consisted of localized areas of more or less complete coagulative necrosis of the mucosa, covered by a layer of fibrin and necrotic debris infiltrated fairly

densely by polymorphs and macrophages (*Fig.* 60). When the necrosis was confined to the superficial parts of the mucosa the openings of the glands of Lieberkühn were occluded by the fibrinous exudate so that secretions were retained, the glands dilated, and the epithelium flattened. Some polymorphs were present in the retained mucus. The submucosa was œdematous and its venules and veins were extremely congested. There were no

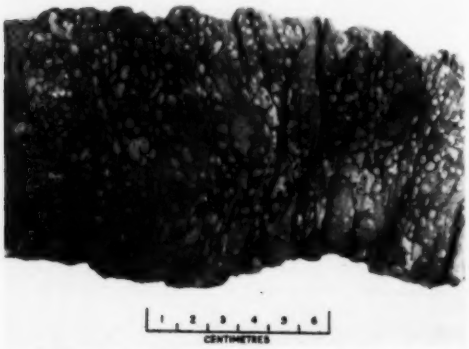

FIG. 59.—*Case* 7. The mucosa and submucosa of the large bowel are œdematous and inflamed, and the surface is studded with innumerable pale, rounded, slightly elevated, adherent plaques. This is an example of the *focal type* of necrotizing enterocolotis.

thrombi in the submucosal venules, but many of the mucosal capillaries in relation to the necrotic areas were plugged by fibrinous thrombi. A sparse infiltrate of polymorphs and macrophages was present in the submucosa and in the muscularis. The serosa was normal.

BACTERIOLOGY.—Numerous bacteria were present on the surface of the mucosa and in the fibrinous exudate over the necrotic lesions in the large bowel, but there was no evidence of invasion of viable tissues. Culture of the intestinal contents and of the exudate over the necrotic lesions gave a growth of coliform bacilli and of enterococci only.

Case 12.—A male of 49 years had complained of periodic dyspepsia of some twenty years' duration and had been in almost constant relapse during the nine months prior to admission to hospital. Radiological examination revealed a large gastric ulcer on the lesser curvature without evidence of malignancy. The patient's general health was good and as there was no apparent contra-indication to operation he was accepted for surgical treatment. Prior to operation it was noted that he was in good nutritional state.

A Billroth-I gastrectomy was done for what was confirmed on subsequent histological examination to be a simple peptic ulcer. The operation was technically straightforward and was completed without incident. The anæsthetic agents given were thiopentone, curare, nitrous oxide, oxygen, and trichlorethylene. Immediately after operation the gastric aspirate contained a considerable amount of fresh blood, and 2 pints of blood were transfused. The patient was not in shock, his pulse-rate rose, but did not exceed 128 per minute. On the morning of the day after operation his general condition gave no cause for anxiety, but as there was still fresh blood in the gastric aspirate it was decided to repeat the blood transfusion and to institute the adrenaline-'stypven' régime described by Brandon (1956). This was repeated later in the day and thereafter the aspirate cleared. On the fourth post-operative day the patient began to pass flatus per rectum, his abdomen was soft and free from tenderness, the pulse-rate was 100/min., and the gastric aspirate consisted of clear bile-stained fluid; gastric suction and intravenous water and electrolyte replacement were discontinued.

At 8 a.m. on the fifth day after operation the patient suddenly became shocked with cold, cyanosed extremities, the pulse was feeble at a rate of 100/min., and the temperature 99·2° F. He was mentally clear and did not complain

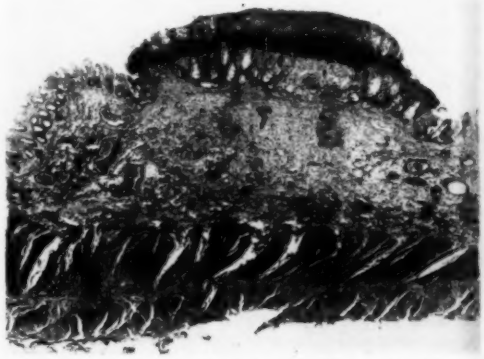

FIG. 60.—*Case* 7. This section through one of the plaques shows that the superficial mucosa is necrotic and covered by fibrinous exudate densely infiltrated by inflammatory cells. This 'pseudomembrane' has blocked the crypts of Lieberkühn and caused retention of secretions. The deeper part of the mucosa and the whole of the underlying submucosa are œdematous, congested, and sparsely infiltrated by inflammatory cells. Picro-Mallory. (× 15.)

of pain. The abdomen was moderately distended, but there was no rigidity and bowel sounds were present. Further bleeding from the gastroduodenal anastomosis was suspected but this was not confirmed by passage of a stomach tube. It was considered that the diagnosis rested between acute necrotizing enterocolitis and a leak from the anastomosis. In the absence of obvious signs of peritonitis the former seemed more probable and treatment was instituted as follows: transfusion of blood followed by Ringer's solution; continuous gastric aspiration; erythromycin intramuscularly; continuous oxygen by BLB mask; cortisone 100 mg., and noradrenaline in the intravenous-drip fluid. Despite these measures shock persisted, the pulse-rate rose, the blood-pressure and temperature fell, but the patient remained mentally alert. At 8 p.m. it was clear that abdominal distension was increasing. Sinus forceps were inserted through the abdominal wound into the peritoneal cavity; foul-smelling gas and a small amount of blood-stained fluid escaped, but there was nothing to indicate an intestinal leak. On the afternoon of the sixth post-operative day a few hours before death, the blood-pressure had fallen to 70/50, pulse-rate 120/min., and temperature 96·8° F. During the 12-hour period prior to death the gastric aspirate was dirty, brown, and foul-smelling.

The most striking features of the clinical picture during the last thirty-six hours of this patient's life were the state of irreversible shock, his lucidity of mind, painless though increasing abdominal distension, and persistent cyanosis despite oxygen therapy.

MORBID ANATOMY.—Autopsy was performed 16 hours after death. The anastomosis between stomach and duodenum was intact, but the duodenum and the loops of jejunum were greatly distended and they were loosely adherent along their lines of contact due to a slight fibrinous exudate. In contrast, the ileum and large bowel were of normal calibre. The gastric remnant contained a little altered blood and its mucosal lining was congested. A small patch of mucosal necrosis was present

on the anterior wall of the stomach. The dilated duodenum and jejunum contained fluid, fæculent material which, in the more proximal loops, was heavily admixed with blood. Similar fluid, fæculent material was present in the ileum. The mucosal lining of duodenum, jejunum, and ileum was intensely hyperæmic but showed no gross evidence of necrosis. The large bowel contained a little fæcal material. The mucosa of the cæcum and of the ascending colon was congested but otherwise appeared normal. In the transverse colon, descending colon, and rectum there were many irregular areas of mucosal necrosis (*Fig.* 61). These necrotic areas ranged in size from a few millimetres to several centimetres in diameter. The intervening mucosa was hyperæmic and œdematous, so that the areas of necrosis were relatively depressed, giving an appearance of ulceration. The edges of the necrotic mucosa were well-defined although irregular in outline. While most of these lesions were a dull yellow others were dark brown due to interstitial hæmorrhage. No readily separable inflammatory membrane was present on the surface. In many places the necrosis could be seen from the serosal surface and had clearly extended more deeply than the mucosa. The mesenteric vessels were normal.

FIG. 61.—*Case* 12. This segment of descending colon shows a discontinuous *patchy type* of necrotizing enterocolitis. The necrotic areas are of varied size and shape and are well demarcated. Although some ulceration has occurred this appearance is accentuated by the œdema and congestion of the surrounding mucosa. A number of these lesions extend through the whole thickness of the bowel wall to the serosa.

There was confluent bronchopneumonic consolidation of the superior segments of the lower lobes of both lungs. The lungs were heavy (right 1700 g., left 1270 g.) due to severe œdema, and a large quantity of frothy fluid was present in the air passages. The kidneys (each 220 g.) were larger than normal due to œdema. Other organs appeared normal.

MICROSCOPICAL FINDINGS.—Examination of the lesions in the stomach and in the distal half of the large bowel showed that they were areas of coagulative necrosis which were generally limited in depth to the whole thickness of the mucosa (*Fig.* 62), but which sometimes extended more deeply to involve even the whole of the muscularis (*Fig.* 63). In the adjacent viable tissue there was a reaction marked by hyperæmia of vessels and an infiltration of polymorphs. When the lesion affected only the mucosa the submucosa was œdematous and fibrinous thrombi were present in many of the venules. The more superficial parts of the necrotic tissue were densely infiltrated by bacteria but none was present in the adjacent living tissues. There was a little fibrinous exudate on the surface of the serosa. Except when it was directly involved in the necrosis there was no notable abnormality of the muscularis. The small intestine and the large areas of stomach and large bowel which were free from necrotizing lesions showed only hyperæmia of the mucosa and submucosa. The kidneys showed changes of the sort that might follow a period of renal cortical ischæmia.

FIG. 62.—*Case* 12. This shows an area of complete coagulative necrosis of rectal mucosa with a sharp transition to relatively normal mucosa. There is a dense inflammatory infiltrate on the deep aspect of the necrotic mucosa and the underlying submucosa is very œdematous and congested. This type of lesion is reminiscent of an ischæmic infarct. Fibrinous thrombi are present in the capillaries of the necrotic mucosa and in the venules on its deep aspect. H. and E. (× 10.)

FIG. 63.—*Case* 12. This necrotizing lesion in the wall of the colon is essentially similar to that illustrated in *Fig.* 62 but has extended much more deeply to involve a considerable thickness of the muscularis. H. and E. (× 10.)

BACTERIOLOGY.—The contents of the stomach and small intestine gave a heavy growth of coliforms and scanty enterococci. A moderately heavy growth of phage-type group III, coagulase-positive *Staph. aureus* sensitive to chloramphenicol and erythromycin was also obtained. A heavy growth of coliforms, *Ps. pyocyanea*, and a light growth of hæmolytic *Cl. welchii* were obtained from the contents of the large bowel.

Case 15.—A male of 41 years was admitted to hospital for surgical treatment of a duodenal ulcer. He gave a history of dyspepsia of some twenty years' duration, perforation four years before his present admission, and for the past year almost constant dyspepsia. The patient was in excellent general health and there was nothing of significance in his past history. An anterior Polya

gastrectomy was done for a large anterior-wall duodenal ulcer associated with considerable pouching and stenosis. The operation was technically straightforward and was completed in 75 minutes with minimal blood-loss.

The immediate post-operative progress was satisfactory, the pulse-rate on the evening of operation being 68 per min. On the morning of the first post-operative day the gastric aspirate was clear and the stomach tube was removed; thereafter limited oral fluids were permitted. The patient passed one loose bowel movement consisting mainly of altered blood and mentioned the expected post-operative 'gas pains', but his general condition remained good throughout the day.

At 4 a.m. on the second day after operation, his pulse was noted by the nurse on duty to be of good quality and she was not concerned about his condition. At 4.30 a.m. she found him in a collapsed state. He was pale and sweating with cold, cyanosed extremities, imperceptible pulse, and unrecordable blood-pressure. Abdominal examination revealed moderate distension but neither rigidity nor appreciable tenderness. The patient was mentally lucid and admitted to occasional abdominal cramps. A diagnosis of acute necrotizing enterocolitis was made, but the possibility of a high intestinal obstruction was not excluded. On the basis of the former diagnosis, infusion of 2 pints of blood followed by noradrenaline drip was started and intravenous erythromycin and hydrocortisone given. Although the blood-pressure was raised to 100 systolic by these measures, the clinical picture of shock persisted. A stomach tube was passed and continuous suction produced large quanties of offensive, dark aspirate. There was no further diarrhœa.

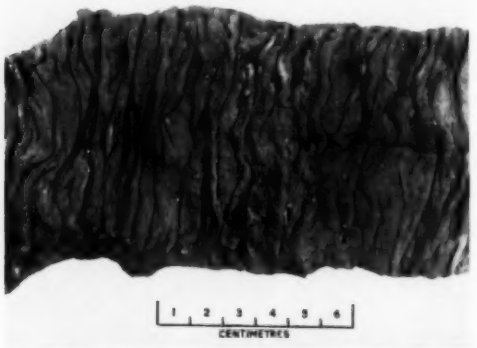

FIG. 64.—*Case* 15. The appearances of this length of jejunum exemplify the *diffuse type* of necrotizing enterocolitis. The whole extent of the mucosa is necrotic to a varying depth and appears dull and opaque. For the most part the necrotic mucosa is still adherent to underlying tissues but it is tending to become detached on the summits of the mucosal folds.

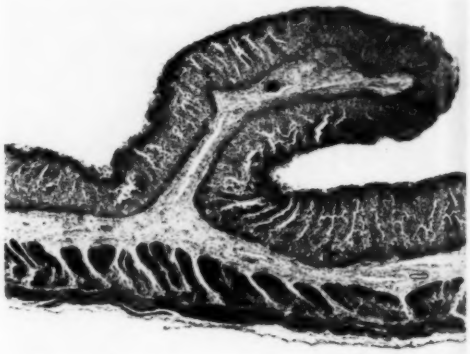

FIG. 65.—*Case* 15. This shows the extensive mucosal necrosis in the jejunum. At the summit of the mucosal fold the whole thickness of the mucosa is necrotic. Elsewhere the deeper parts of the crypts are still identifiable. There is very little fibrinous exudate on the surface. A fibrinous thrombus can be seen in a submucosal venule. Masson. (× 15.)

FIG. 66.—*Case* 15. This shows in more detail than *Fig.* 65 the complete hæmorrhagic necrosis of the mucosa at the summit of a mucosal fold. The fibrinous thrombi in mucosal capillaries and venules are clearly evident. Again it is notable that there is little inflammatory exudate on the surface. P.T.A.H. (× 40.)

At 4 p.m. it was thought advisable to perform laparotomy to exclude intestinal obstruction. The wound was reopened; the gastrojejunal anastomosis and the duodenal stump closure were intact; the entire small bowel was distended and bluish-purple, this unhealthy discoloration being most marked in the distal ileum; there was no mechanical obstruction. These findings seemed to support the diagnosis of acute necrotizing enteritis, and intravenous fluid and electrolyte replacement with added noradrenaline, erythromycin, and hydrocortisone was continued. Oxygen therapy did not relieve the patient's cyanosis and hyperpnœa. He died at 8.30 p.m. on that day.

MORBID ANATOMY.—Autopsy was performed 13 hours after death. The peritoneal sac contained a small quantity of blood-stained fluid. There was no evidence of peritonitis and the anastomoses were intact. The gastric remnant was a little dilated and contained yellowish watery fluid but its mucosal lining showed no gross abnormality. The whole of the small intestine was considerably dilated and the serosa was generally purplish in colour. The contents were similar to those of the stomach and there was no admixture of blood. The mucosa of the duodenum and of the first loops of jejunum was extremely congested and on the surface of the mucosal folds there were small plaques of loosely adherent yellowish exudate. Throughout the remainder of the jejunum and ileum the mucosa had the opaque yellowish appearance of necrosis (*Fig.* 64). In the ileum the necrotic mucosa was only loosely adherent and had begun to peel off spontaneously, exposing the deeply congested

Table I.—Clinical Features of 16 Cases of Acute Necrotizing Enterocolitis

Case No.	Year	Age and Sex	Pre-existing Disease	Operation	Antibiotic	Onset of Symptoms (days post-op.)	Clinical Features	Day of Death (days post-op.)
1	1940	36 M.	Acute intestinal obstruction	Enterostomy	None	—	Admitted with severe abdominal pain and sickness for 5 days. Collapsed and dehydrated. No diarrhœa. Abdomen tympanitic. Patient severely shocked.	2
2	1944	66 M.	Strangulated inguinal hernia	Reduction and repair	None	Uncertain	Vomiting and diarrhœa without abdominal pain. Sudden collapse	10
3	1950	65 M.	Pyloric stenosis	Gastro-enterostomy	None	3	Complained of abdominal discomfort. Sudden peripheral circulatory failure	3
4	1952	53 M.	Gastric ulcer	Partial gastrectomy	None	3	Tachycardia, abdominal pain, hypotension. Diarrhœa and collapse. No response to I.V. fluids	4
5	1953	60 M.	Carcinoma of stomach	Gastrectomy and partial hepatectomy	None	3	Abdominal distension for 48 hours. Sudden collapse. No response to I.V. fluids and methedrine. No diarrhœa	5
6	1956	52 M.	Para-œsophageal hernia	Repair of hernia	None	3	Sudden collapse. Peripheral circulatory failure. Diarrhœa. Abdominal distension. Hyperpyrexia. No response to I.V. fluids, blood transfusion, or noradrenaline	4
7	1956	50 M.	Mitral stenosis Exfoliative dermatitis Pneumonia Myocardial infarction	None	Tetracycline 500 mg. 6-hourly for 2 days. 250 mg. 6-hourly for 3 days	—	Sudden collapse with extreme peripheral circulatory failure. Diarrhœa with greenish stools. No response to I.V. fluids or noradrenaline: hyperpyrexia	2*
8	1956	67 M.	Duodenal ulcer Pyloric stenosis	Gastrectomy and removal of head of pancreas	Penicillin 500,000 units b.d. for 5 days. Streptomycin 0·5 gm. b.d. for 1 fday	?	Gradual deterioration. No evidence of sudden collapse. No diarrhœa. Paralytic ileus. Temperature to 103° F.	7
9	1956	38 M.	Appendicitis with abscess	Appendicectomy. Drainage of abscess	Chlortetracycline 250 mg. 6-hourly for 5 days	5	Sudden onset of peripheral circulatory failure. Partial response to I.V. fluids and noradrenaline. No diarrhœa. Collapsed again	6
10	1956	54 M.	Gastric ulcer	Partial gastrectomy	None	3	Patient got out of bed. Slight diarrhœa, sudden collapse	3
11	1956	27 F.	Inevitable abortion	Dilatation and curettage	None	2	Patient shocked; oliguria; jaundice. No response to plasma transfusion and noradrenaline	2
12	1956	49 M.	Gastric ulcer	Partial gastrectomy	None	5	Sudden collapse and cyanosis following administration of enema. Abdominal distension. No response to blood transfusion, I.V. fluids, cortisone, and and noradrenaline	6
13	1956	53 M.	Duodenal ulcer Pyloric stenosis	Gastro-enterostomy; vagotomy	None	3	Sudden collapse. Blood-pressure 65/30. No diarrhœa. Abdomen not distended. No fever. Laparotomy — resection of gangrenous jejunum	4
14	1956	63 M.	Myocardial infarction	None	Tetracycline 100 mg. I.M. b.d. for 3 days	—	Continuing low blood-pressure after infarction. Peripheral circulatory failure. Anuria. Rectal bleeding	5*
15	1957	41 M.	Duodenal ulcer	Partial gastrectomy	None	3	Mild post-operative diarrhœa. Sudden collapse with peripheral circulatory failure. No response to transfusion and noradrenaline. Laparotomy. Hyperpyrexia.	3
16	1957	51 M.	Perforated duodenal ulcer	Closure of perforation	None	2	Passage of frequent, small, fluid stools. Profound degree of shock. Systolic blood-pressure 80	3

* Days after onset of symptoms.

submucosa. The cæcum, colon, and rectum were almost empty, apart from some watery, yellowish fluid, and they showed no mucosal necrosis or other gross abnormality. There was no evidence of occlusion of the mesenteric vessels. The lungs (right 870 g., left 800 g.) were heavy, due to congestion and œdema, and muco-pus was present in the trachea and bronchi. The heart appeared normal apart from the presence of numerous subepicardial petechiæ over the right auricle and ventricle. Other organs showed no notable abnormality.

MICROSCOPICAL FINDINGS.—The jejunum showed a hæmorrhagic necrosis of the whole superficial third of the mucosa (*Fig.* 65). On the summits of the mucosal folds the necrosis extended through the entire thickness of the mucosa and sometimes involved even the muscularis mucosæ. There was only slight surface exudate and no notable reaction on the deep aspect of the necrotic tissue, which suggested that the condition was of very recent development. Capillaries and venules related to the necrotic mucosa were almost invariably filled with fibrinous thrombi (*Fig.* 66). The submucosa was œdematous and sparsely infiltrated by lymphocytes and polymorphs. The muscle coat showed interstitial œdema and many of the muscle cells were swollen and hyaline in appearance. The nerve plexuses and the serosa were normal. The appearances in the ileum were essentially similar, but generally the whole thickness of the mucosa was necrotic and there was a thin layer of fibrinous exudate on its surface. Gram-stained sections showed a variety of organisms on and in the necrotic mucosa. The stomach and colon showed no notable abnormality.

BACTERIOLOGY.—A heavy growth of *Proteus* and coliforms was obtained from the jejunum together with a fairly heavy growth of hæmolytic and non-hæmolytic *Cl. welchii*. Using fluid media with added NaCl, coagulase-positive *Staph. aureus* of phage-type groups *II* and *III* was also isolated and was found to be resistant to penicillin, chlortetracycline, oxytetracycline, and streptomycin but sensitive to chloramphenicol and erythromycin. Staphylococci with these characteristics were also present in the gastric aspirate before death. The ileal contents yielded a heavy growth of *Proteus* and coliforms, and a moderate growth of hæmolytic and non-hæmolytic *Cl. welchii*.

CLINICAL OBSERVATIONS

The clinical findings of the 16 cases are summarized in *Table* I and are well illustrated by the three cases described in detail above. In 14 instances acute necrotising enterocolitis followed a surgical operation; in 2 patients it was a sequel to myocardial infarction. Operations on the stomach preceded the onset of the enterocolitis in 8 cases, gastrectomy in 6 cases, and gastro-enterostomy in 2 cases, in one of which it was combined with vagotomy. In the other six surgical cases a variety of operations was done (*see Table I*).

The outstanding clinical feature was the development of acute peripheral circulatory failure. This was noted in all except one of the cases. In the majority the onset was sudden. This was most striking in *Case* 10. This patient had a remarkably smooth post-operative course after gastrectomy and was getting out of bed on the third day when she suddenly collapsed with profound peripheral circulatory failure and was dead within a few hours. In the other surgical cases the immediate post-operative course was not always so smooth, but in all there was a sudden change in the patient's condition, usually on the second or third post-operative day, but in two cases on the fifth day. In one of the medical cases the patient made a good initial recovery from his myocardial infarction but two days later an acute collapse with peripheral circulatory failure followed; in the other the blood-pressure remained low after the infarction and signs of shock persisted until death. In most of the cases it was recorded that in spite of a profound degree of peripheral circulatory failure the patients remained mentally clear and alert. In the majority of cases this acute peripheral circulatory failure did not respond to treatment by the most energetic measures designed to overcome shock. The signs of peripheral circulatory failure persisted till death, which occurred from six to forty-eight hours after the onset of the acute symptoms in all cases. A striking feature in several cases was an intense cyanosis of the extremities such as is described in the case reports.

Diarrhœa was a prominent symptom in only four cases and in another two there was slight diarrhœa. In *Case* 14 there was some rectal bleeding, but it was thought that this was probably due to the anti-coagulants which the patient was receiving for his myocardial infarction. In the other cases the clinical picture suggested intestinal obstruction of the paralytic type. Pain was not a prominent feature; severe abdominal pain was noted in *Case* 1 and abdominal discomfort associated with diarrhœa was present in two cases but in the others the condition was relatively painless. Distension of the abdomen was observed in only four cases. Fever was not marked in the majority of the cases, but in four there was a terminal hyperpyrexia.

Anuria was associated with the acute peripheral circulatory failure in three cases but in at least one it was known that the patient continued to secrete urine until death although there was profound hypotension for more than forty-eight hours.

Four patients only had received antibiotics before the onset of their acute symptoms. Two patients had a short course of tetracycline and one a similar course of chlortetracycline; the fourth received only penicillin until the day before death when he was also given streptomycin. In none of these cases were the drugs given for more than five days and the dosage was relatively small in each case.

PATHOLOGICAL OBSERVATIONS

Morbid Anatomy.—The gross morbid anatomical appearances in our cases varied considerably according to the extent and distribution of the lesions. In some cases the whole intestinal tract and even the stomach were extensively or completely involved. In other instances the lesions were limited to either the small or the large bowel (*see Table II*). Within the affected segments the necrotizing process was sometimes continuous, sometimes patchy and irregular, and in two cases focal. For these reasons it is not possible to give a comprehensive description which will fit all cases.

It was common, however, to find considerable dilatation of the affected part of the bowel especially when the small intestine was involved. Externally the bowel presented a dusky purplish appearance due to intense hyperæmia and stasis. There was often a small amount of sero-sanguineous fluid in the peritoneal sac. In the lumen of the small bowel there was usually a greatly increased content of fluid fæculent material often more or less heavily admixed with blood.

The large bowel, on the other hand, was frequently empty apart from an excessive secretion of mucus which might be bile-stained.

When mucosal necrosis was well established the appearances were unmistakable. The necrotic mucosa was usually a dull yellow, but might be stained green by bile or be dark brown if there had been much extravasation of blood into the dead tissues. Together with any exudate which had formed on the surface this necrotic mucosa constituted a 'pseudomembrane' which might be firmly adherent, loosely attached, or even have been shed spontaneously into the lumen.

In early cases, on the other hand, the mucosal necrosis was often barely recognizable on naked-eye examination and the appearances were simply those of œdema and congestion. In some cases in which advanced necrotizing lesions were present in the large bowel the small intestine was notably dilated and its mucosal lining œdematous and hyperæmic although there was no evidence of necrosis. When the necrotic process was circumscribed and patchy in distribution, there seemed to be a tendency for a greater depth of the wall to be involved. The dull yellowish necrotic areas were then clearly evident on

Table II.—SALIENT PATHOLOGICAL CHANGES AND BACTERIOLOGICAL FINDINGS

CASE	PATHOLOGY	BACTERIOLOGY
1	Diffuse mucosal necrosis with pseudomembranous inflammation of *ileum*. Jejunum dilated, wall intensely congested and œdematous	No record
2	Multiple foci (up to 1·0 cm. diameter) of mucosal necrosis with pseudomembranous inflammation in *pelvic colon* and *rectum*	No 'intestinal pathogens' isolated
3	Necrosis and pseudomembranous inflammation on summits of mucosal folds of *small intestine*—not evident on naked-eye examination. Mucosa intensely congested. Bowel contents blood-stained	Heavy growth of *Cl. welchii* and of non-hæmolytic streptococci from intestinal contents
4	Extensive mucosal necrosis with fibrinous exudation throughout *large intestine*	No 'specific intestinal pathogens' isolated
5	Extensive mucosal necrosis of *jejunum*. Remainder of bowel grossly normal (not examined microscopically)	Cultures not made
6	Extensive mucosal necrosis and pseudomembranous inflammation of *jejunum*, *ileum*, and *large intestine*	Normal bowel flora of enterococci and coliforms with scanty heat-sensitive type -A *Cl. welchii*.
7	Numerous foci (up to 0·5 cm. diameter) of mucosal necrosis and pseudomembranous inflammation throughout *large intestine*	Normal intestinal flora of coliforms and enterococci
8	Extensive mucosal necrosis of *stomach* and of the circular folds of *jejunum*; almost total necrosis of a 4·0 cm. length of *transverse colon*	Heavy growth of coliforms, non-hæmolytic streptococci and *Neisseria*. Scanty *Cl. welchii*
9	Extensive mucosal necrosis and pseudomembranous inflammation of *jejunum* and *proximal ileum*	Cultures not made, but numerous staphylococci seen on section, in the exudate
10	Multiple small foci of acute mucosal necrosis in *duodenum*. Remainder of bowel grossly normal but not examined microscopically	Cultures not made
11	Patchy mucosal necrosis in *rectum*, extending deeply into muscularis in places. Remainder of bowel grossly normal but not examined microscopically	Cultures not made
12	Patchy necrosis of mucosa of *stomach*, *descending colon* and *rectum* extending more deeply in places. The mucosal lining of whole intestinal tract is intensely congested	Heavy growth of coliforms, *Ps. pyocyanea*, and light growth of hæmolytic *Cl. welchii* from colonic contents. In stomach and jejunum heavy growth of coliforms and scanty enterococci; also moderately heavy growth of phage-type group III coagulase-positive *Staph. aureus*
13	Numerous irregular almost confluent areas of mucosal necrosis in *ileum*, *descending colon*, and *rectum* often invading deeper layers of bowel wall	Heavy growth of coliforms and hæmolytic *Cl. welchii*, also scanty enterococci, from contents of small and large intestine both before and after death. No *staphylococci isolated* despite particular search
14	Extensive mucosal necrosis of *descending colon* and *rectum* with areas of deeper involvement	Heavy growth of coliforms and scanty enterococci. Heavy growth of hæmolytic *Cl. welchii*. Slight growth of coagulase-positive *Staph. aureus*, phage-type group III, in fluid media with added NaCl
15	Very extensive mucosal necrosis of *jejunum* and *ileum* with slight fibrinous exudate	Coagulase-positive *Staph. aureus* grown in fluid media with added NaCl from gastric aspirate before death and from jejunum after death—phage-type group II and III. Heavy growth of coliforms, *Proteus*, and *Cl. welchii* (hæmolytic and non-hæmolytic) throughout intestine
16	Extensive mucosal necrosis and pseudomembranous exudate in *ileum*. Patchy mucosal congestion in *jejunum* and *colon*	Moderate growth monilia, scanty *Cl. welchii* and coagulase-positive *Staph. aureus* (phage-type group III) from jejunum. Moderate growth *Ps. pyocyanea* from ileum

the serosal aspect of the bowel where they were often associated with a fibrinous exudate. In our experience it was unusual for the stomach to be involved but when it was the gross features were similar to those seen in the intestine. *Cases* 2 and 7 were somewhat different from the others in that the lesions were small, rounded, sharply circumscribed and very numerous; in both cases these focal lesions were confined to the large bowel. Apart from their size and shape, however, the gross appearance of the lesions was comparable to that seen in other cases.

Microscopical Findings.—These also varied in detail from case to case but there appeared to be a basic similarity in the pathological changes observed. The outstanding feature was necrosis of the bowel wall limited to the mucosa in the majority of cases. This mucosal necrosis was of the coagulative variety so that although cellular details were lost, the general architectural features were often largely preserved. In the earliest recognizable stages necrosis was confined to the summits of mucosal folds. At a later stage the whole superficial part of the mucosa might be necrotic while the basal parts of the crypts still appeared viable. In such cases, where the depth of necrosis was slight, there was usually a fibrinous exudate on the surface forming a coagulum in which inflammatory cells, mainly polymorphs and macrophages, were enmeshed. This fibrinous 'pseudomembrane' often blocked the exit of secretions from the surviving crypt cells so that the crypts were distended with mucin in which polymorphs might be present. When the whole thickness of the mucosa was necrotic, exudation of fibrin occurred, if at all, into the dead tissue rather than on the surface. In the necrotic mucosa it was often possible to distinguish the outlines of dilated capillaries filled with fibrinous thrombi.

The submucosa underlying the necrotic areas was usually œdematous and there was dilatation, frequently extreme, of venules and veins. In all cases there was a sparse inflammatory infiltrate of polymorphs and macrophages throughout the submucosa, but in immediate relationship to the deep aspect of the necrotic layer the inflammatory cells were often more densely concentrated, giving an appearance reminiscent of that seen at the margin of an ischæmic infarct. A further notable feature in the submucosa was the presence of fibrinous thrombi in many of the dilated venules. In contrast, thrombi were never found in the arterioles.

The muscle coat and the nerve plexuses usually showed no notable abnormality apart from slight œdema and a sparse inflammatory infiltrate. Occasionally, however, the muscle coat was also affected by the process of coagulative necrosis. The serosa was usually normal but in some cases its vessels were hyperæmic and some fibrinous exudate was present on the surface. Those parts of the bowel lying between or adjacent to necrotic areas usually showed œdema and hyperæmia of the mucosa and submucosa and evidence of excessive mucus secretion, i.e., acute catarrhal inflammation.

Bacteriology.—Gram-stained sections of the bowel showed a variety of gram-positive and gram-negative bacteria in large numbers on the surface of the necrotic mucosa and in any exudate which might be present. Bacteria were always present but scanty, within the necrotic tissue and a few were usually to be found in immediately adjacent viable tissues. Special staining methods gave no indication that the necrotic lesions were due to the presence of fungi or of protozoal organisms. Cultural examination of bowel contents in our earlier cases was usually performed with the purpose of isolating one of the known intestinal pathogens, but more recently attention has been directed to the possible role of other organisms such as coagulase-positive *Staph. aureus* or food-poisoning varieties of *Cl. welchii*. The detailed findings in our cases are recorded in *Table II*, and the implications of these findings are discussed below.

DISCUSSION

Nomenclature.—All of our cases have been characterized by necrosis of the inner layer of the bowel wall. The necrosis may be focal, patchy, or diffuse and, although usually confined to the mucosa, may extend more deeply. Nevertheless, this mucosal necrosis, almost invariably associated with thrombotic occlusion of the related capillaries and venules, was the one pathological feature common to all cases. Superficial inflammatory exudation was not a constant finding although in many cases it did constitute a distinct pseudomembrane. Accordingly, we have preferred to describe the condition as *acute necrotizing enterocolitis* in preference to the more widely used term 'pseudomembranous enterocolitis' or the older term 'diphtheritic enterocolitis'.

There has been an increasing tendency in recent publications to use the term 'staphylococcal pseudomembranous enterocolitis' or some similar variant (Williams, 1954; Speare, 1954; Corridan, 1956). This, however, has questionable aetiological implications and on the basis of our own experience and that of others (Fowler, 1955; Dearing, 1956) we would endorse the opinion expressed by Weismann and Twitchell (1956) that "until more convincing evidence is presented to incriminate this organism (i.e., *Staph. aureus*) it would seem better to identify the disease by its pathological characteristics than to becloud its nature with bacteriologic or other pseudonyms".

Clinical Aspects.—Recently a number of publications have appeared on the subject of acute necrotizing or pseudomembranous enterocolitis (Pettet, Baggenstoss, Dearing, and Judd, 1954; Dawson-Edwards and Morrissey, 1955; Hultborn, 1956; Newman, 1956). These have dealt mainly with the condition as a post-operative complication, which is its commonest mode of occurrence. As in the present series, the majority of writers have found that the operation which is most frequently followed by this serious condition is partial gastrectomy. A notable exception is the report by Pettet and others who found that the condition occurred most commonly after operations on the colon. But it may occur after any intra-abdominal procedure and has been reported occasionally following other operations. That acute necrotizing enterocolitis can also occur in association with certain non-surgical conditions was pointed out by Kleckner and others (1952). They described 14 cases in which the onset of the condition was not preceded by any surgical operation. In seven of these

the acute necrotizing enterocolitis was the cause of death, in the other seven it was regarded as an incidental finding. The pre-existing conditions in their series were intestinal obstruction in 5 cases, cardiac disease in 5 cases, and infections in 4 cases. In three of the cardiac cases the disease was coronary atheroma with myocardial infarction and in the other two it was chronic rheumatic endocarditis, lesions similar to those which were present in the two medical cases in the present series. It is unusual for acute necrotising enterocolitis to present as a primary condition but 2 cases have been described by Hultborn (1956). Thus the present series of cases may be regarded as a representative sample of the clinical conditions in which acute necrotizing enterocolitis may be encountered.

Hultborn expresses the view that the disease occurs especially in patients in a poor nutritional condition. This has not been our experience. A number of our patients were previously healthy young adults and the older patients were all considered to be in good general health. In none of the surgical cases did the surgeon or the anæsthetist express any concern about fitness for operation.

In the surgical cases the immediate post-operative course is either uneventful or at least not associated with any more serious disturbance than might be expected after a major abdominal operation. The onset of the disease occurs suddenly between the second and the fifth post-operative day and the first sign is usually the development of acute peripheral circulatory failure. Diarrhœa is an inconstant feature, but when present may be severe and choleriform in type. In the large series reported by Pettet and others (1954) diarrhœa was observed in less than half the cases and Newman (1956) also mentions that it is not invariably present. The outstanding clinical feature is the rapid onset of a state of profound shock, which has not responded to the most energetic measures designed to overcome it. In our experience this state of shock has always been associated with a remarkable degree of mental alertness similar to that described by Grant and Reeve (1951) in patients suffering from wound shock. Other findings, such as abdominal pain and distension, hyperpyrexia, and anuria due to the catastrophic fall in blood-pressure, may occur, but are by no means constant.

Causation and Pathogenesis.—

General.—First we must consider to what extent we are justified in regarding our cases as comprising a single disease entity. Although the clinical features are fairly characteristic they are not specific, and a clinical diagnosis of necrotizing enterocolitis can seldom be more than presumptive. The pathological changes in the bowel are striking and follow a common basic pattern, but they, too, cannot be regarded as unique. Changes of a similar kind can be produced in various parts of the gastro-intestinal tract by a number of agencies, for example infections (bacillary dysentery), chemical poisons (mercury, arsenic), and uræmia (Cappell, 1951). To confirm the diagnosis it is necessary to consider both the clinical and the pathological features. Pending more definite knowledge of causation than is at present available we believe that it is justifiable to regard our post-operative cases as variants of a single disease. We also believe that the non-surgical cases are sufficiently similar to justify their inclusion in the same group. Some workers may have been too indiscriminate in their diagnosis of this condition, often relying on clinical features alone or including cases which have lacked the characteristic necrotizing lesions in the bowel (*see*, for example, Dawson-Edwards and Morrissey; Hultborn). As a result of this practice it is probable that there has often been failure to distinguish between the two conditions of staphylococcal enteritis and acute necrotizing enterocolitis (*see* below).

Shock.—This has long been regarded as an important causal condition. Penner and Bernheim (1939) considered that the bowel lesions were essentially a form of ischæmic necrosis of the mucosa due to the vasomotor disturbances associated with shock. Later this opinion was reiterated by Penner and Druckerman (1948). In conformity with Dixon and Weismann (1948) we are unable to confirm this hypothesis. In our post-operative cases the indications are that circulatory failure was a consequence rather than the cause of the bowel lesions. In none of these cases, nor in the majority of those reported in the literature, have we been able to find evidence of any lesion other than the changes in the bowel which could account for the sudden development of acute peripheral circulatory failure. Nor are we familiar with any report which describes the lesions of acute necrotizing enterocolitis in man occurring in association with shock due to other causes, e.g., wound shock. Two of our non-surgical cases (*Cases* 7 and 14) were suffering from acute myocardial infarction and it is conceivable that in one of them severe cardiac failure might have resulted in such marked vasoconstriction as to determine an ischæmic necrosis of the bowel mucosa, just as in other cases it may cause acute ischæmic damage in the kidneys or gangrene of the extremities. In the other case, however, the patient had made a good immediate recovery from his infarction and the episode of acute peripheral circulatory failure was not associated with any evidence of further infarction. It is notable that many of the non-surgical cases reported in the literature have been associated with some form of heart disease.

Local Vasomotor Disturbances.—These, or vascular occlusions, must also be considered as a cause of mucosal ischæmia, and the histological appearance of the bowel lesions is certainly often consistent with an ischæmic necrosis. The almost invariable finding of fibrinous thrombi in capillaries and venules related to the necrotic areas is in keeping with this explanation, although it could also be regarded as a secondary phenomenon. McKay, Hardaway, Wahle, and Hall (1955) succeeded in producing widespread thrombosis in the mucosal capillaries of the gastro-intestinal tract in dogs by introducing quantities of human blood into the aorta in the region of the mesenteric arteries. They found that the animals died within two to three hours of the injection and autopsy showed areas of superficial necrosis of the intestinal mucosa associated with a pseudomembrane. Although this work may point the way to further experimental studies its bearing on the condition of necrotizing enterocolitis in man is uncertain.

It has recently been shown that the vascular arrangements in the bowel wall are such that shunting of the blood could occur so as to by-pass the mucosa (Boulter and Parkes, 1957). Whether or not this could take place to the extent of cutting off the mucosal blood-supply is unknown, and the nature of the stimuli which might determine such an event is quite obscure.

Relationship to the Use of Antibiotics.—The condition of necrotizing enterocolitis has come into much greater prominence in the last decade and the reputed increase in incidence has been widely attributed to the increasing use of antibiotics. Reiner, Schlesinger, and Miller (1952), for example, reported 7 cases of 'pseudomembranous colitis' following the use of chlortetracycline (5 cases) and chloramphenicol (2 cases) but were unable to explain the pathogenesis. More recently Hartman and Angevine (1956) reported 17 cases of 'pseudomembranous colitis' following prolonged antibiotic therapy, and diagnosed at autopsy. They suggested that the condition they were describing differed from post-operative enterocolitis in being focal in distribution and more or less confined to the large bowel. One of our non-surgical cases (*Case* 7) resembled these closely and was on tetracycline therapy, but on the other hand exactly similar lesions were present in one of our surgical cases (*Case* 2) in which antibiotics were not administered. While we agree that this focal type of lesion differs from that seen in the majority of our cases we are not convinced that it is fundamentally different. Furthermore, many of the alleged post-antibiotic cases have in fact been of the diffuse variety (for example, the case of Corridan, 1956).

Hartman and Angevine made the interesting suggestion that antibiotics destroy the normal bowel flora and favour the growth of vitamin-requiring organisms such as *Staph. aureus* and *Proteus vulgaris*. A vitamin deficiency results, and deficiency of pantothenic acid in particular might cause 'pseudomembranous colitis'. The bowel changes described by Wintrobe, Follis, Alcayaga, Paulson, and Humphreys (1943) in swine reared on a diet deficient in pantothenic acid do not really resemble those of necrotizing enterocolitis in man, and in any case they develop only after a latent period of at least four weeks. The suggestion of Helmer (1954) that necrotizing enterocolitis may be due to an allergic reaction to antibiotics is purely speculative.

Before ascribing an aetiological significance to antibiotics it should be noted that necrotizing enterocolitis was recognized, particularly as a post-operative complication, for many decades before their introduction (Penner and Bernheim, 1939). Kleckner and others (1952) observed that there had been no increase in the incidence of acute fatal pseudomembranous enterocolitis in the files of the Mayo Clinic since the introduction of antibiotics and chemotherapeutic agents in the treatment of intestinal disorders. Likewise Pettet and others (1954) reporting 94 fatal post-operative cases from the Mayo Clinic between 1925 and 1952 could find no evidence that the condition was related to the use of antibiotics. Prohaska and others (1954), on the basis of 7 personally observed cases, doubt whether pre-operative use of antibiotics is an aetiological factor. Our own experience leads us to believe that antibiotics play no notable part in the causation of necrotizing enterocolitis, as in only 4 cases were antibiotics administered prior to the onset of the condition (*Table I*). The fact that we have seen more cases in recent years we attribute largely to an increased awareness of the condition.

Infective Hypothesis.—Many of those who subscribe to the view that necrotizing enterocolitis is related to the use of antibiotics believe that the explanation lies in the occurrence of 'super-infection' whereby an infectious process develops due to the growth of resistant bacteria. Particularly following the use of the broad-spectrum antibiotics there is a high incidence of diarrhœa and in many of the more severe cases coagulase positive *Staph. aureus* has been cultured from the stool. There has grown up, as a result of this, the concept of staphylococcal enteritis as a 'super-infection' complicating antibiotic therapy, in which it is suggested that enterotoxin-producing strains of *Staph. aureus* are actually growing in the gut (Surgalla and Dack, 1955). Numerous cases of staphylococcal enteritis following the use of various antibiotics have now been recorded and it is noteworthy that in most of them the morbid anatomical changes in the bowel are not those of necrotizing enterocolitis. There may be mucosal hyperæmia and even catarrhal inflammation, but mucosal necrosis with membranous inflammation is not generally a feature (*see*, for example, the reports of Gardner, 1953; Hay and McKenzie, 1954; Kramer, 1948; Cunningham and Beavan, 1955; and Fowler, 1955). In a recent report by Cook, Elliott, Elliot-Smith, Frisby, and Gardner (1957) only 2 out of 14 autopsied cases of 'staphylococcal diarrhœa' showed the features of pseudomembranous enterocolitis. We have ourselves encountered cases of post-antibiotic diarrhœa in which *Staph. aureus* was grown in almost pure culture from the stool, but in which at autopsy, there was no evidence of necrotizing enterocolitis.

Brodie, Kerr, and Sommerville (1956) found that the fæcal carrier-rate for enterotoxin-producing strains of *Staph. aureus* in hospital patients increased from 5 per cent to 35 per cent within seven days of admission. It follows that the mere presence of staphylococci in the bowel contents from cases of necrotizing enterocolitis, even in large numbers (Todd and Hopps, 1955), does not necessarily indicate their aetiological importance. Furthermore, there is good evidence that in some cases of necrotizing enterocolitis staphylococci are not present in the bowel contents or in the inflammatory membrane (Rieckert, 1955). We recognize, however, that in the past the presence of staphylococci may have been overlooked through failure to employ the appropriate techniques for their isolation (Cook and others, 1957). In our own series coagulase-positive *Staph. aureus* was present in moderate numbers in 4 cases and in 3 of these was found to be of phage-type group III, i.e., the strain commonly found in the fæces and sometimes associated with food-poisoning (Anderson and Williams, 1956). In another case numerous clusters of gram-positive cocci were seen in the pseudomembrane in histological sections, but cultures were not made. In only one case can it be asserted that staphylococci were definitely absent

(*Table II*). There is need for a much wider experience of cases investigated by adequate bacteriological technique in order to assess the frequency with which staphylococci are associated with the condition of necrotizing enterocolitis and in what proportion they are present in relation to other intestinal bacteria.

Dearing and Heilman (1953) have also recorded cases of pseudomembranous enterocolitis in which staphylococci were not present in the bowel and, conversely, fatal cases of staphylococcal enteritis with no evidence of mucosal necrosis and pseudomembranous inflammation. In yet other cases pseudomembranous enterocolitis was associated with the presence of large numbers or even pure cultures of staphylococci. Dearing (1956) has confirmed and extended these observations and his findings are similar to ours. In five of his cases of pseudomembranous enterocolitis there were no staphylococci in the intestine. Dearing and Heilman inferred that pseudomembranous enterocolitis and staphylococcal enteritis are probably two essentially unrelated conditions although they may occur together It is also possible, however, that their association, when it does occur, is not simply fortuitous, but that the changes in the intestine which determine the occurrence of necrotizing enterocolitis may be initiated in some way by an attack of staphylococcal enteritis, just as by various other conditions. Cases such as that described by Friedell and Paige (1954) lend support to this view.

Attempts to reproduce the condition of necrotizing enterocolitis experimentally, by introducing staphylococci obtained from human cases into the alimentary tract of various animals, have proved unsuccessful (Prohaska, Long, and Nelsen, 1956). On the other hand a *spontaneous* outbreak of 'staphylococcal enterocolitis' has now been described by Wood, Bennett, and Yardley (1956) in a colony of chinchillas which had been fed on pellets containing a small quantity of chlortetracycline. They believe that the condition is the counterpart of acute necrotizing enterocolitis in man, but on the evidence so far available it appears to us that there are several important differences. The long latent period (of twelve months) after chlortetracycline was introduced into the diet, before cases appeared in the colony of chinchillas, raises the possibility that vitamin deficiency may have played some part (*see* Hartman and Angevine, 1956). We are also not convinced that the pathological changes in the bowel are similar to those found in man. At present the hypothesis that necrotizing enterocolitis is directly due to infection of the bowel by entero-toxin-producing strains of *Staph. aureus* must be regarded as unproven and indeed there is considerable circumstantial evidence against the acceptance of this concept.

Less attention appears to have been paid to the possibility that other bacteria might be the cause of the variety of necrotizing enterocolitis with which we are concerned. In 1946, Beckerman and Laas described several cases of a fulminating and often fatal variety of primary necrotizing enterocolitis occurring in Hamburg. Their description of the pathological changes in the bowel closely parallels that of the cases which we have reported in this paper. A similar condition was reported by Jeckeln (1947, 1948) from Lübeck and was given the name of "Darmbrand". Fick (1947) and Fick and Wolken (1949) described what was probably the same condition as 'necrotic jejunitis'. Zeissler and Rassfeld-Sternberg (1949) working in Hamburg, examined the intestinal contents from twelve such cases of necrotizing enteritis and isolated from all of them an organism "closely resembling *Cl. welchii*" which they named *Cl. welchii* type F. They believed that this organism might be important in the causation of the disease. Outbreaks of this condition appear to have been confined to North Germany and no evidence has been forthcoming to incriminate *Cl. welchii* type F as the cause of necrotizing enterocolitis elsewhere.

It is known that other varieties of *Cl. welchii* can behave as intestinal pathogens under certain circumstances. For example, non-hæmolytic strains of *Cl. welchii* type A appear to have been responsible for some outbreaks of food-poisoning (Hobbs, Smith, Oakley, Warrack, and Cruickshank, 1953), and it is established that *Cl. welchii* type D is the cause of enterotoxæmia of sheep (Bennetts, 1932) and possibly of intestinal disturbances in man (Kohn and Warrack, 1955). In view of the fact that many of our cases have followed partial gastrectomy, and that Howie, Duncan, and Mackie (1953) found *Cl. welchii* in the stomachs of a high proportion of patients in the first week after this operation, a special search has been made in our more recent cases for the presence of these various types of *Cl. welchii*. Non-hæmolytic strains of *Cl. welchii* type A have been found in the intestinal contents of only a few of our cases, and in none of them have types D or F been identified (*Table II*).

There is at present no direct evidence to support the suggestion of Hormann (1947) that the disease may be due to a virus infection, but the possibility should be considered, particularly in view of the observations of Dow, Jarrett, and McIntyre (1956) who have described a virus disease in cattle in which one of the manifestations is necrosis of the intestinal mucosa.

Diagnosis.—The typical clinical picture is that of a patient between the second and fifth day after operation who is mentally clear and alert, with minimal abdominal signs, extreme cyanosis of the extremities, a rapid pulse of poor volume, and a blood-pressure which is very low or even unrecordable. If diarrhœa is present bacteriological examination of the fæces may reveal the presence of staphylococci, particularly if antibiotics have been administered. In any event, the implications of their presence are uncertain and as the condition constitutes a grave emergency treatment must be instituted without delay and certainly before a bacteriological report can be obtained. A similar clinical picture characterized by sudden and severe shock may result from high intestinal obstruction in the immediate post-gastrectomy period (Stammers, 1957). The only satisfactory method of distinguishing between these two conditions is by laparotomy and we believe that even if a diagnosis of acute necrotizing enterocolitis has been made on clinical grounds, laparotomy should be advised at once. If an obstruction is found the patient's life may be saved; if acute necrotizing enterocolitis is the cause of the shock-like state, it is

unlikely that laparotomy will influence the course of the disease.

Therapeutic Aspects.—

Prophylaxis.—Since doubt exists regarding the aetiology of acute necrotizing enterocolitis doubt must also exist regarding prevention. According to individual views, emphasis will tend to be placed on measures designed to combat shock or on measures directed towards the control of infection and toxæmia. In the present state of our knowledge and faced with a condition of such grave import, it is probably expedient to employ all forms of therapy which at one time or another have been advised by various authorities on the basis of individual experience.

Although we are convinced that the pre-operative use of antibiotics is not a direct cause of necrotizing enterocolitis we believe that emphasis should be placed on warning against their indiscriminate use because of the risk of staphylococcal enteritis. If these agents have to be employed they should be discontinued at the earliest possible moment. In the pre-operative preparation of cases for intestinal surgery the relatively insoluble sulphonamides should be used whenever possible.

In surgical cases every care should be taken regarding good technique, gentle handling of the intestine, careful hæmostasis at suture lines, and meticulous sterilization of stomach tubes. Post-operative dilatation of the gut can be prevented by continuous gastric aspiration and this should always be continued until active bowel sounds have returned. It is clearly of the utmost importance to institute therapy for shock at the earliest possible moment, and any blood lost at operation should always be replaced. Hypokalæmia with its liability to produce atony of the intestine should be prevented and if it should develop it must be treated as early as possible.

Treatment.—We have been concerned mainly with the problem of acute necrotizing enterocolitis as a post-operative complication, especially after operations on the stomach. Our depressing experience has been that once the patient has entered the stage of acute peripheral circulatory failure, which is most often the presenting feature of the condition, all our therapeutic measures have been ineffective. In this we are not alone, as in most of the reported cases the diagnosis has been established post mortem. Three of the seven cases of post-operative 'pseudomembranous enterocolitis' described by Prohaska and others (1954) recovered after treatment with corticotrophin, but we are not convinced that these three patients were suffering from the condition with which we are familiar; their symptoms developed at a later stage (10 to 30 days after operation) and the authors mention that shock was not a prominent clinical feature of the illness. Nyhus and Burke (1954) reported the case of a 9-year-old boy who developed severe pseudomembranous enterocolitis after the prolonged administration of chlortetracycline for pneumonia. The clinical picture in this case was similar to that which we have observed in our patients. The boy recovered after intensive treatment with blood transfusion, massive intravenous fluids, noradrenaline, hydrocortisone, and erythromycin. Christianson, Dacquisto, and Dobbs (1954) described a single patient who presented a similar clinical picture, also after the prolonged administration of chlortetracycline for pneumonia. Their patient received only massive intravenous fluids and erythromycin, and also recovered. In our recent cases we have instituted the following régime promptly and enthusiastically. Any antibiotics being given have been stopped at once and, on the possibility that a resistant staphylococcus may be present, erythromycin has been substituted. Shock has been treated by intravenous therapy including blood, fluid containing specific electrolytes, noradrenaline, and by administration of hydrocortisone. If gastric aspiration has been discontinued it is recommenced. Oxygen therapy has also been employed.

We have no experience of the use of the antihistamine group of drugs as suggested by Helmer (1954) on the basis that acute necrotizing enterocolitis is the result of an antigen–antibody response. As there is no indication that *Cl. welchii* type F plays any part in the causation of necrotizing enterocolitis in this country we have not used polyvalent anti-gas-gangrene serum as suggested by Zeissler and Rassfeld-Sternberg (1949).

SUMMARY

1. The clinical and pathological features of 16 fatal cases of acute necrotizing (pseudomembranous) enterocolitis are presented.

2. Fourteen of the cases followed surgical operations; in two the enterocolitis occurred in patients with heart disease.

3. The operation which most frequently preceded the condition was gastrectomy.

4. The outstanding clinical feature is the rapid development of a state of irreversible acute peripheral circulatory failure. Diarrhœa is an inconstant feature, but is sometimes severe. Symptoms develop from two to six days after operation and all our patients died within forty-eight hours of the onset.

5. The most prominent pathological feature is necrosis of the intestinal mucosa associated with thrombotic occlusion of the related capillaries and venules. The changes may be widespread, localized, or focal in distribution and they may occur in any part of the small or large intestine and occasionally in the stomach.

6. The causation and pathogenesis of the condition are considered in detail and the question of nomenclature is discussed.

7. It is thought that the enterocolitis is the cause of and not a sequel to the acute peripheral circulatory failure.

8. The relationship of the disease to the use of antibiotics is considered and the opinion is expressed that there is no good evidence to support the hypothesis that necrotizing enterocolitis is directly due to the use or abuse of these drugs.

9. The association of the condition with staphylococcal infection of the bowel is discussed. Staphylococcal enteritis and acute necrotizing enterocolitis are probably not directly related although they may occur together.

10. In the post-operative cases the clinical diagnosis between acute necrotizing enterocolitis and high small bowel obstruction is difficult; immediate laparotomy is therefore advised.

11. Treatment for shock and the administration of erythromycin and adrenal hormones have so far proved ineffective.

We wish to express our thanks to the physicians, surgeons, and pathologists who have given us access to their records. In particular, we wish to acknowledge the help given by Miss E. J. McKillop, who was responsible for the bacteriological investigation of many of our more recent cases. The photographs were taken by Mr. G. Kerr.

REFERENCES

ANDERSON, E. S., and WILLIAMS, R. E. O. (1956), *J. clin. Path.*, **9**, 94.

BECKERMAN, F., and LAAS, E. (1946), *Ärztl. Wschr.*, **1**, 329.

BENNETTS, H. W. (1932), *Bull. Coun. sci. industr. Res. Aust.*, No. 57.

BOULTER, P. S., and PARKES, A. G. (1957), personal communication.

BRANDON, W. J. M. (1956), *Lancet*, **1**, 360.

BRODIE, J., KERR, MARY R., and SOMMERVILLE, T. (1956), *Ibid.*, **1**, 19.

BRUCE, J. (1955), *Proc. R. Soc. Med.*, **48**, 245.

CAPPELL, D. F. (1951), *Muir's Text-book of Pathology*, 6th ed., p. 584. London: Arnold.

CHRISTIANSON, C. S., DACQUISTO, M. P., and DOBBS, W. H. (1954), *Gastroenterology*, **26**, 645.

COOK, J., ELLIOTT, C., ELLIOT-SMITH, A., FRISBY, B. R., and GARDNER, A. M. N. (1957), *Brit. med. J.*, **1**, 542.

CORRIDAN, M. (1956), *J. Clin. Path.*, **9**, 131.

CUNNINGHAM, J. A. K., and BEAVAN, D. W. (1955), *N. Z. med. J.*, **54**, 644.

DAWSON-EDWARDS, P., and MORRISSEY, D. M. (1955), *Brit. J. Surg.*, **42**, 643.

DEARING, W. H. (1956), *Ann. N.Y. Acad. Sci.*, **65**, 235.

— — and HEILMAN, F. R. (1953), *Proc. Mayo Clin.*, **28**, 121.

DIXON, C. F., and WEISMANN, R. E. (1948), *Surg. Clin. N. Amer.*, 28, **999**.

DOW, C., JARRETT, W. F. H., and MCINTYRE, W. I. M. (1956), *Vet. Rec.*, **68**, 620.

FICK, K. A. (1947), *Z. ges. inn. Med.*, **2**, 447.

— — and WOLKEN, A. P. (1949), *Lancet*, **1**, 519.

FOWLER, R. J. (1955), *Brit. med. J.*, **1**, 1313.

FRIEDELL, G. H., and PAIGE, E. (1954), *Amer. J. clin. Path.*, **24**, 1159.

GARDNER, D. L. (1953), *Lancet*, **2**, 1236.

GRANT, R. T., and REEVE, E. B. (1951), "*Observations on the General Effects of Injury in Man*", *Spec. Rep. Ser. med. Res. Coun.*, No. 277. London: H.M.S.O.

HARTMAN, H. A., and ANGEVINE, D. M. (1956), *Amer. J. med. Sci.*, **232**, 667.

HAY, P., and MCKENZIE, P. (1954), *Lancet*, **1**, 945.

HELMER, F. (1954), *Wien. klin. Wschr.*, **66**, 120.

HOBBS, B. C., SMITH, M. E., OAKLEY, C. L., WARRACK, G. H., and CRUICKSHANK, J. C. (1953), *J. Hyg., Camb.*, **51**, 75.

HORMANN, H. (1947), *Ärtzl. Wschr.*, **2**, 998.

HOWIE, J. W., DUNCAN, I. B. R., and MACKIE, L. M. (1953), *Lancet*, **2**, 1018.

HULTBORN, K. A. (1956), *Acta chir. scand.*, **111**, 29.

JECKELN, E. (1947), *Dtsch. med. Wschr.*, **72**, 105.

— — (1948), *Ibid.*, **73**, 177.

KLECKNER, M. S., BARGEN, J. A., and BAGGENSTOSS, A. H. (1952), *Gastroenterology*, **21**, 212.

KOHN, J., and WARRACK, G. H. (1955), *Lancet*, **1**, 385.

KRAMER, I. R. H. (1948), *Ibid.*, **2**, 646.

MCKAY, D. G., HARDAWAY, R. M., WAHLE, G. H., and HALL, R. M. (1955), *Arch. intern. Med.*, **95**, 779.

NEWMAN, C. R. (1956), *Ann. intern. Med.*, **45**, 409.

NYHUS, R. E., and BURKE, E. C. (1954), *Proc. Mayo Clin.*, **29**, 513.

PENNER, A., and BERNHEIM, A. A. (1939), *Arch. Path. (Lab. Med.)*, **27**, 966.

— — and DRUCKERMAN, L. J. (1948), *Gastroenterology*, **11**, 478.

PETTET, J. D., BAGGENSTOSS, A. H., DEARING, W. H., and JUDD, E. S. (1954), *Surg. Gynec. Obstet.*, **98**, 546.

PROHASKA, J. V., GOVOSTIS, M. C., and TABENHAUS, M. (1954), *J. Amer. med. Ass.*, **154**, 320.

— — LONG, E. T., and NELSEN, T. S. (1956), *Arch. Surg., Chicago*, **72**, 977.

REINER, L., SCHLESINGER, M. J., and MILLER, G. M. (1952), *Arch. Path. (Lab. Med.)*, **54**, 39.

RIECKERT, P. (1955), *Dtsch. med. Wschr.*, **80**, 855.

SPEARE, G. S. (1954), *Amer. J. Surg.*, **88**, 523.

STAMMERS, F. A. R. (1957), *Brit. J. Surg.*, **44**, 358.

SURGALLA, M. J., and DACK, G. M. (1955), *J. Amer. med. Ass.*, **158**, 649.

TODD, A. S., and HOPPS, P. O. D. (1955), *Lancet*, **2**, 749.

WEISMANN, R. E., and TWITCHELL, E. B. (1956), *Ann. Surg.*, **144**, 32.

WILLIAMS, E. (1954), *Lancet*, **2**, 999.

WINTROBE, M. W., FOLLIS, R. H., ALCAYAGA, R., PAULSON, M., and HUMPHREYS, S. (1943), *Bull. Johns Hopk. Hosp.*, **73**, 313.

WOOD, J. S., BENNETT, I. L., and YARDLEY, J. H. (1956), *Ibid.*, **98**, 454.

ZEISSLER, J., and RASSFELD-STERNBERG, L. (1949), *Brit. med. J.*, **1**, 267.

RENAL FAILURE DUE TO PERI-URETERIC FIBROSIS

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THE recent paper by Raper (1956) has stimulated interest in this condition and it seemed worth recording a further case, one which embodied certain special features.

In this condition a diffuse mat of fibrous tissue develops in the retroperitoneal space immediately in front of the posterior abdominal wall. Although the term 'peri-ureteric fibrosis' has been commonly used, the area of fibrous tissue involves also the great vessels and may, in fact, produce vascular symptoms quite apart from ureteric obstruction. Ureteric involvement has, however, occurred more frequently than vascular obstruction and has been more dramatic in its manifestations.

FIG. 67.—I. V. P., March, 1956. Normal pyelographic appearances.

FIG. 68.—I. V. P., July, 1956. No dye concentration by either kidney.

The cause of the disease is unknown and the fibrous tissue when sectioned shows no especial features. On the other hand the effects are serious and may well be fatal if a correct diagnosis is not made. It seems likely that the disease has been overlooked in the past and may have been responsible for a number of deaths. Raper (1956) has pointed out that the reported cases fall into two fairly well-defined groups:—

1. Those associated with acute renal pain, and
2. Those developing renal failure in the course of a vague illness.

To the two groups must be added a third category in which the ureters escape and obstruction of the large vessels causes claudication or other symptoms of vascular origin.

In the first group a bilateral hydronephrosis may be revealed by investigation, or one kidney may not be functioning. In the second it is usually found that neither kidney is functioning on intravenous pyelography and it is probable that one kidney has not been functioning for a considerable time; anuria thus results from failure of the only functioning kidney. An interesting feature in both groups is that it may be possible to pass a catheter up the ureter, and this might be misleading except for the fact that the passage of the catheter is followed by a profuse flow of urine, demonstrating that there is indeed, an obstruction. It is probable that the fibrosis, invading the ureteric wall, interferes with peristalsis rather than producing an actual constriction. This point was well shown in the case reported below. This patient was of interest for the following reasons:—

1. It was possible to demonstrate that the disease progressed from normality to a moderate degree of renal failure within a matter of several weeks.
2. A pre-operative diagnosis was made.
3. As a result of treatment both kidneys have apparently made a complete recovery.
4. Hydrocortisone was used, possibly for the first time, in this condition.

CASE REPORT

A male, aged 49 years, who had previously enjoyed good health, began to feel generally unwell and to complain of pains in the back on both sides and also in the

left testis. In addition there was diurnal frequency and moderate nocturia. An intravenous pyelogram proved normal in all respects (*Fig.* 67); the urine was sterile, and it was thought that he had a transient urinary infection which was subsiding.

His symptoms continued intermittently for the succeeding few weeks, gradually becoming worse, the pain being principally confined to the right flank and

FIG. 69.—Right retrograde pyelogram. Partial obstruction noted in the mid-portion of the ureter and dilatation of the calyces.

now accompanied by loss of weight and loss of appetite, with nausea and vomiting. Twelve weeks after the initial investigation his condition necessitated his admission to hospital.

On examination some tenderness was found in the right loin and small bilateral hydroceles were present. The blood-pressure was 160/90. An intravenous pyelogram showed no function in either side (*Fig.* 68) and no dye was seen in the bladder. The N.P.N. was 81 mg. per cent, the B.S.R. 48 mm. in the first hour but the urine contained no organisms, albumin, or casts. The urea concentration was 0·75, 0·73, 0·72, and 0·84 urea g. per cent.

At cystoscopy the bladder appeared normal but, after injection of dye, only a faint trace of blue was seen from the right ureter in fourteen minutes. A size 10 ureteric catheter passed readily up to the right kidney and it was noted that there was a free flow of clear urine under considerable pressure from the catheter. The catheter was withdrawn to the lower third of the ureter and the opaque medium injected. Severe and characteristic pain was experienced on injection and there appeared to be a definite obstruction of the ureter at the level of L.3 and 4, on pyelography (*Fig.* 69). It was impossible to fill the kidney completely from the ureter but there did not appear to be any calyceal dilatation.

There appeared to be no doubt that there was an obstruction in the middle third of the right ureter and, in view of the extreme rapidity of the renal failure, a tentative diagnosis of peri-ureteric fibrosis was made. In the light of subsequent events it would seem that the testicular pain and small hydroceles were significant clinical features. This point has not been made in any previous communication on this subject.

The right kidney was therefore exposed and was found to be somewhat indurated and œdematous. Biopsy, however, revealed no evidence of nephritis. There was a dense mat of fibrous tissue in the retroperitoneal region, obscuring the great vessels and extending downwards as far as the brim of the pelvis. The upper two-thirds of

FIG. 70.—I. V. P., August, 1956. Return of function to the right side two weeks after ureterolysis.

the ureter was embedded in a groove of fibrous tissue (*Fig.* 72) from which it was separated (*Fig.* 73) except at the upper end, where it was tethered by a strand of blood-vessels. Even when dislodged from the groove the ureter still felt like a hard cord. Further stripping of fibrous tissue from the adventitia finally gave it the consistency of normal ureter (*Fig.* 74). Some extraperitoneal fat was stitched into the groove and oily hydrocortisone placed around the ureter. The wound was closed with drainage. A few days later a course of hydrocortisone was commenced, being continued until 400 mg. had been given.

Two weeks after the operation an intravenous pyelogram showed excellent function on the right but still no function on the left (*Fig.* 70). The N.P.N. had fallen to 34 mg. per cent.

Operation on the left side was performed through a Rutherford Morrison incision a fortnight after the exploration of the right ureter. The upper half of the ureter was firmly embedded in a mass of fibrous tissue, which was so dense in places that it had a neoplastic appearance. The ureteric involvement extended from the pelvic brim upwards to stop abruptly at the pelviureteric junction, which was normal. When the ureter was liberated it appeared as a rope-like cord which was 'decorticated', long strips of fibrous tissue being readily removed (*Fig.* 73). It has been suggested that the correct method is to place the ureter in the peritoneal cavity, but this procedure was impossible here as it would have necessitated the ureter traversing a dense fibrous plaque adherent to the peritoneum, near the renal pelvis. Accordingly the outer wall of the fibrous groove was

excised and the extraperitoneal and perirenal fat were stitched to the psoas, on the outer side of the groove, the ureter being displaced laterally towards the outer border of the psoas muscle.

Biopsy specimens revealed œdematous fibrous tissue with chronic inflammatory cells. In some places the fibrous tissue was undergoing hyaline degeneration (*Fig.* 76).

FIG. 71.—I. V. P., September, 1956. Return of function to the left kidney following ureterolysis on that side.

FIG. 72.—Operation. Left ureterolysis. The ureter encased in fibrous tissue is exposed.

FIG. 73.—Operation. Left ureterolysis. The fibrous sheath being stripped off the ureter.

Two weeks after the second operation an I.V.P. revealed normal function of both kidneys (*Fig.* 71). A urea-concentration test was reported on as follows: 1·32, 2·17, 2·10, and 2·20 urea g. per cent.

An apparently complete recovery ensued. The N.P.N. changes are shown on the graph (*Fig.* 75).

REVIEW OF THE LITERATURE

In 1948 Ormond reported 2 cases in which there was bilateral ureteric obstruction due to an enveloping and compressing inflammatory retroperitoneal process. Since then a further 22 case histories of patients manifesting similar features have appeared in the literature. The youngest patient was 24 years of age and the oldest 69 years, with the majority in the fourth decade. Males predominated in the ratio 2:1.

The essential pathology is the appearance in the retroperitoneal area of fibrous tissue in intimate relationship to the structures of the posterior abdominal wall. Invariably involvement of the ureter by the fibrosis results in the patient presenting with urinary symptoms so that a diagnosis, if made at all, is suggested by means of a urological investigation. Implication of the urinary tract, however, appears to be secondary, merely incidental and not selective. Instances of involvement of other retroperitoneal structures have been encountered. Raper (1956) cites 2 cases in which there was coincident vascular occlusion, and describes terminal jaundice in another consequent upon compression of the extrahepatic bile-ducts. Chisholm, Hutch, and Bolomey (1954) attributed œdema of the leg and scrotum in their patient to compression of the inferior vena cava. Operative exploration of a mass palpable in the left upper quadrant of the abdomen revealed fibrosis enveloping the kidney, adrenal, spleen, and tail of pancreas in the case of Paull, Causey, and Hodges (1955). In the 4 examples quoted by Vest and Barelare (1953) the pathological tissue was described as being confined to a sheath around the ureter. They designated the condition 'periureteritis plastica', seeing in some of its features an analogy with linitis plastica. Raper in his paper excludes these four cases from the collected series, suspecting that they represented a different disease entity on the grounds of the localization of the fibrosis and histological details. It is possible, however, that these differences may be merely variants on a main pathological theme, as the case histories of these particular patients contain several features similar to those of the group as a whole.

Histological reports all describe fibroblasts, collagen fibres, and round-cell infiltration, the last comprising polymorphonuclear leucocytes, plasma

cells, and lymphoid follicles. Ormond refers to the density of the collagen tissue and was reminded of the appearance of keloid. The abundance of fibroblastic activity caused Bradfield (1953) to query a sarcoma of low-grade malignancy. Ewell and Bruskewitz (1952) found arteriolitis in their sections.

FIG. 74.—Operation. Left ureterolysis. The ureter has been completely freed and displaced from its original position.

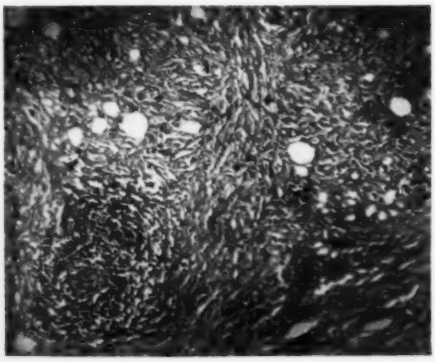

FIG. 76.—Histological appearances of the tissue removed at ureterolysis, showing fibrous stroma containing vascular spaces and a small round-cell infiltration.

Most authors comment on the inflammatory appearance of the tissue and in the case of Miller, Lipin, Meisel, and Long (1952), frank small abscesses were present. These were unfortunately not cultured, but antibiotics were administered with successful results as far as clinical recovery was concerned.

The aetiology is unknown and a matter for speculation. Maclean's patient (1954) had a history of a blow in the abdomen inflicted by a baseball several years previously, and the advent of retroperitoneal fibrosis was thought to be explicable on the basis of organization of a hæmatoma. The popular view supports an inflammatory origin with which the microscopical appearance is consistent. As no organisms have been isolated in any of the reported cases the fibrosis must be the end-result of an infection overcome by the natural defences of the host if the lesion is a response to bacterial invasion. Houston (1957) reconciled the inflammatory appearance and absence of organisms by regarding the condition as an infective granuloma, the outcome of an infection aborted by chemotherapy. He recalled the better-known antibiotic granuloma of treated breast abscesses. In this respect it is worthy of note that

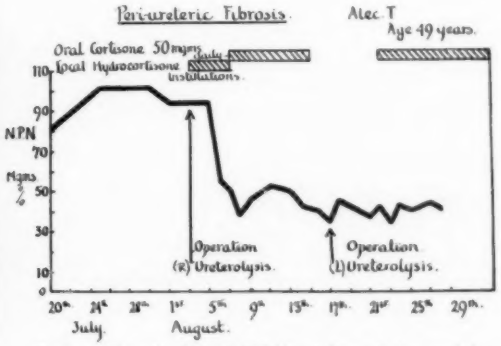

FIG. 75.—Record of blood N.P.N. readings during period of hospital treatment.

retroperitoneal fibrosis has only been recognized since the introduction of modern antibacterial therapy.

Apart from obstruction of the ureter following inflammation in adjacent bowel, e.g., regional ileitis and diverticulitis, Chisholm and others (1954) suggest that the retroperitoneal space may be infected via the lymphatics draining the intestine. To explain the distribution of the fibrosis they quote the anatomical finding of Daseler and Anson (1943) that the ureters, great vessels of the posterior abdominal wall, and the lymph-glands draining the bowel are in the same fascial compartment. Raper, repeating study on this theory, could not confirm the fact.

Vest and Barelare (1953) attribute the periureteric localization of the pathological tissue in their case to periureteric lymphangitis and suggest the lower genito-urinary tract as the site of ingress of infection. Anastomotic channels between the lymphatics of the lower urinary tract and the ureter, as demonstrated experimentally by Winsbury-White (1933), are held to be the route of spread. In this connexion 6 patients in the series had a history of previous urinary pathology.

Pain and urinary symptoms are the presenting features in many of these patients. The pain is variable both in location and severity. When situated in the loin it may be a dull ache or a typical renal colic, with radiation into the genitalia and thigh. Aching pain in the lumbosacral region, hypogastrium, and testicle has also been described.

Hæmaturia and the advent of anuria are the main urinary disturbances reported, whilst frequency and dysuria have been less common. Episodes of frank bleeding occurred in 5 patients and in a further 3 cases red blood-cells were found on microscopy of the urine. Anuria supervened at some stage of the disease in 5 cases and was the outcome of bilateral fibrous involvement of the ureters. Chronic ill

health, loss of weight, anæmia, pyrexia, and anorexia are all features of variable incidence.

Clinical examination of the patient may be unrewarding. However, it was possible to appreciate the retroperitoneal fibrosis as a tumour on abdominal palpation in the patient of Miller and others (1952). Reference has already been made to the mass palpable in the left upper quadrant in Paul's patient. Tenderness and pain in the loin have frequently been noted and correlate with the subsequent disclosure of hydronephrosis and impaired renal function on that side. In isolated instances œdema of the legs, hydroceles, and jaundice have been interpreted as being due to compression of other retroperitoneal structures.

Laboratory findings in the urine are inconstant. Specimens may show no abnormality or contain a trace of albumin, a few leucocytes, or red blood-cells. A positive culture was obtained in 3 cases. In patients in whom the ureteric compression is bilateral, with consequent anuria or evidence of impaired renal function, a raised blood-urea is a not unexpected finding. Drainage of the renal pelvis in the anuric patient via a ureteric catheter is a life-saving measure and was necessary for both of Ormond's original cases as a prelude to further surgery. In any event the disclosure of upper urinary tract obstruction is the indication for operative intervention. In the collected series ureterolysis was carried out on 20 ureters in 14 patients. Ureterolysis is not always feasible and this is well illustrated by 2 of Raper's cases in which the fibrosis was found to be inseparably blended with the wall of the ureter and causing a stricture in a localized segment which required resection and anastomosis. Chisholm and others combined a temporary nephrostomy with a ureterolysis. Having freed the ureter the problem of preventing it being caught up again in a desmoplastic process has been met by displacing the ureter into a new position within the peritoneal cavity (Ormond, 1948).

Ewell and Bruskewitz (1952) carried out a preliminary nephrostomy on the remaining kidney of their patient before exploring the ureter and freeing it from its fibrous sheath six weeks later, following which the nephrostomy rapidly closed.

Radiotherapy has been used post-operatively to discourage reactionary fibrosis (Ormond, 1948; Oppenheimer, Narins, and Simon, 1952).

There has been no case report to date recording the use of cortisone in the management of retroperitoneal fibrosis. Cortisone could not be expected to act as a substitute for surgery as fibrous tissue already formed would not be affected by the corticosteroids. As a means of preventing a fibrotic reaction after ureterolysis, however, it has much to recommend it on theoretical grounds. Furthermore the application of cortisone in preventing recurrent strictures elsewhere in the urinary tract has a successful precedent in the experience of Baker, Govan, and Huffer (1952), who noted both on experimental and clinical grounds the inhibitory effect of cortisone on urological strictures.

SUMMARY

1. A case of periureteric fibrosis is presented in which a correct pre-operative diagnosis enabled bilateral ureterolysis to be performed with a successful outcome.

2. Attention is drawn to testicular pain and vaginal hydroceles as being additional clinical features of periureteric fibrosis.

3. It is suggested that cortisone may be a useful adjunct to ureterolysis in the treatment of this condition.

4. Previous case reports on the subject are reviewed.

Acknowledgements.—It is a pleasure to record our gratitude to Professor C. A. Wells, who saw the patient in consultation; and Mr. F. M. Parsons, of the Department of Urology, Leeds General Infirmary, for his helpful comments on the case.

Appreciation is also accorded to Dr. Nancy Bun for the Spanish translation of one of the references and to Mr. Lee, of the Central Photographic Department, University of Liverpool, for the illustrations.

REFERENCES

ANSELEM, A. (1950), *Med. esp.*, **23**, 230.
BAKER, R., GOVAN, D., and HUFFER, J. (1952), *Surg. Gynec. Obstet*, **95**, 446.
BRADFIELD, E. C. (1953), *J. Urol.*, **69**, 769.
CHISHOLM, E. R., HUTCH, J. A., and BOLOMEY, A. A. (1954), *Ibid.*, **72**, 812.
DASELER, E. H., and ANSON, B. J. (1943), *Ibid.*, **49**, 789.
EWELL, G. H., and BRUSKEWITZ, H. W. (1952), *Urol. cutan. Rev.*, **56**, 3.
HOUSTON, W. (1957), *Brit. J. Urol.*, **29**, 28.
IOZZI, L., and MURPHY, J. J. (1957), *J. Urol.*, **77**, 402.
MACLEAN, J. T. (1954), *Brit. J. Urol.*, **26**, 127.
MILLER, J. M., LIPIN, R. J., MEISEL, H. J., and LONG, P. H. (1952), *J. Urol.*, **68**, 447.
MIRABILE, C. S., and SPILLANE, R. J. (1955), *Ibid.*, **73**, 783.
OPPENHEIMER, G. D., NARINS, L., and SIMON, N. (1952), *Ibid.*, **67**, 476.
ORMOND, J. K. (1948), *Ibid.*, **59**, 1072.
PAULL, D. P., CAUSEY, J. C., and HODGES, C. V. (1955), *Ibid.*, **73**, 212.
RAPER, F. P. (1956), *Brit. J. Urol.*, **28**, 436.
VEST, S. A., and BARELARE, B. (1953), *J. Urol.*, **70**, 38.
WINSBURY-WHITE, H. P. (1933), *Brit. J. Urol.*, **5**, 249.

HYPERPLASTIC TUBERCULOSIS OF THE DISTAL COLON

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INTRODUCTION

INCREASING knowledge of the different types of intestinal granulomata has resulted in a critical assessment of the diagnosis of hyperplastic or hypertrophic productive tuberculosis. This lesion is said to occur in the ileo-cæcal region in 85 per cent of cases (Bockus, 1944). Well-documented reports of involvement of the distal colon are rare. The literature on this subject is summarized in *Table I*. It will be seen that confirmation of the diagnosis by acid-fast stains, culture, and guinea-pig inoculation has only rarely been carried out. Discussion of the pathology in many cases has been lacking or scanty and in these cases the diagnosis can only be regarded as presumptive. Eight of the sixty-three cases reported were associated with carcinoma of the colon or rectum. Cases of diffuse involvement of the colon as reported by Lockhart Mummery (1923) and Bockus, Tumen, and Kornbloom (1940) are not included in this review.

It is unlikely that hypertrophic tuberculosis of the distal colon is as uncommon as this review of the literature would suggest. I feel, therefore, that a full report is required of the following two cases which I have treated in this hospital during the past three years.

CASE REPORTS

Case 1.—J. P., a female aged 10 years was admitted to the Christian Medical College Hospital on Oct. 4, 1954 with a history of periodic umbilical pain and diarrhœa for the past six months. The pain was colicky in nature, coming on an hour after eating food and was relieved by passage of fæces or flatus. There had never been any blood in the stools and there were no urinary symptoms.

ON EXAMINATION.—She was a well-nourished young girl in fairly good general condition. Conjunctivæ were pale. Cardiovascular and respiratory systems were normal. Blood-pressure was 100/80. Examination of the abdomen revealed no physical signs apart from slight generalized distension. Hæmoglobin was 7·75 g. E.S.R.—first hour 45, second hour 85. PPD reaction was positive. Radiograph of the chest: "Heavy shadows and increased markings towards the upper zones. No infiltrations are seen." Barium meal (*Fig.* 77): "Narrowing of four inches of transverse colon with some dilatation beyond this seen at 6 hours. Narrowing is still present at 24 hours and is well demonstrated by air insufflation at this time. Probable tuberculous stricture of transverse colon".

AT OPERATION (Oct. 13, 1954 (D.M.H.)).—Laparotomy. Excision of stricture of pelvic colon with end-to-end anastomosis. Obstructive resection of stricture of transverse colon by Paul-Mickulicz method.

Findings.—Two narrowed segments were found in the colon—one at the middle of the transverse colon and one at the junction of the descending and sigmoid colon. Both segments were about 2 in. long with nodularity and thickening of the overlying peritoneum and bowel wall at these sites. There were clusters of enlarged regional lymph-nodes in the mesentery at both sites. The specimens were opened and ulceration was found to extend on either side of the two constricted areas. Hæmorrhagic areas and multiple small nodules were found at the periphery of the ulcers. The other viscera were normal. This operation was followed by an uneventful convalescence and the colostomy was closed on Nov. 10. The patient was discharged on Nov. 23 in good health.

FOLLOW-UP.—The patient was last seen in April, 1957. She was keeping well and was gaining weight. Bowels were regular. There had been no recurrence of symptoms.

FIG. 77.—*Case* 1. Barium meal follow-through radiograph (6 hours). Narrowing of the transverse colon well shown.

HISTOLOGY.—The peritoneal coat is markedly thickened by chronic inflammatory cells and fibrous tissue. The muscular coat shows hypertrophy and foci of epithelioid cells and giant cell systems. The mucosa shows ulceration and crypt abscesses. Lymph-nodes show tubercular giant cell systems and epithelioid cells with minimal caseation. Acid-fast bacilli were demonstrated on tissue staining.

SUMMARY.—Hyperplastic tuberculosis of colon with lymph-node involvement.

Comment.—This case was admitted with mild symptoms of obstruction due to the constricting lesions in the colon. Both lesions in the transverse and pelvic colon were excised at the same operation, and this was followed by an uneventful recovery and follow-up over two and a half years. Examination of the bowel lesion showed a non-specific inflammation of the entire thickness of the bowel wall as is found in regional colitis (Neuman and Dockerty, 1954). Evidence for the tuberculous nature of the lesion was only found after careful search of the lymph-nodes had revealed caseating tubercles and acid-fast bacilli.

Case 2.—J. Y., a male aged 24 years, was admitted to the Christian Medical College Hospital on July 5, 1956

Table I.—PUBLISHED CASES OF HYPERPLASTIC TUBERCULOSIS OF THE DISTAL COLON†

AUTHOR	DATE	SITE IN COLON	NO. OF CASES	BASIS FOR DIAGNOSIS	HISTOLOGICAL CONFIRMATION
* Mayo	1899	Sigmoid	2		
Archibald	1920	Sigmoid	1		Patient stated to have pulmonary T.B. No discussion of pathological details
* Caird	1921	Transverse	2		Hyperplastic lesion
* Lockhart Mummery	1923	Sigmoid	6	Operation	Hyperplastic lesions
* Mailer	1927	Sigmoid	2		Two cases of diverticulitis of sigmoid associated with T.B.
* Yeomans	1929	Sigmoid	1		
Bargen, Copeland, and Rankin	1930	Sigmoid	2	Barium enema and laparotomy	Sigmoid lesions not visualized in either case. Tuberculous peritonitis present in both cases and confirmed by biopsy in one
Dowdle	1930	Descending	1	Laparotomy and lymph-node biopsy	Gland biopsy showed "early tubercle" formation. No mention made of presence or absence of caseation
* Anderson and Munro	1931	Transverse	2		
* Cooper	1932	Sigmoid (tuberculosis and carcinoma) Sigmoid (tuberculosis and carcinoma)	4 4		Cases of tuberculosis and carcinoma occurring side by side
Rankin and Major	1932	Transverse Sigmoid	1 1	Operation	No discussion of pathological details
Davis	1933	Sigmoid	3	Operation	No discussion of pathological details
Miller	1936	Descending (tuberculosis and carcinoma)	1	Autopsy	Case of tuberculosis and carcinoma of descending colon. Associated active pulmonary T.B. with cavity of right upper lobe. No mention of caseation or acid-fast bacilli
* Cullen	1940	Sigmoid	1	Autopsy	
Frimodt-Moller	1943	Descending	1	Barium enema	
Randall and Spalding	1946	Splenic flexure (tuberculosis and carcinoma)	1	Operation specimen	Case of tuberculosis and carcinoma. Areas of caseation found and tubercle bacilli seen with acid-fast stain
Adams and Miller	1946	Sigmoid	5	Operation	Four cases were associated with fæcal fistulæ. Two of these cases later developed "diffuse involvement of colon". No discussion of pathological details
Kornblum, Zale, and Aronson	1948	Transverse Descending Sigmoid	6 6 4	Autopsy	No discussion of histology. All had pulmonary T.B. Some of these cases may have been instances of secondary ulcerative colitis (tuberculous)
Banerjea	1950	Ileo-cæcal region with numerous "skip lesions" in colon	1	Not mentioned	No discussion of pathological details
Hickinbotham	1950	Ileo-cæcal region and sigmoid (plus carcinoma of rectum)	1	Autopsy	Separate ulcero-hypertrophic tuberculous lesions of ascending colon and sigmoid. No mention of caseation or acid-fast bacilli. Associated active T.B. cavitation of left apex and separate carcinoma of rectum
Rappaport, Burgoyne, and Smetana	1951	Hepatic and splenic flexure	1	Operation specimen	Hyperplastic lesions with minimal caseation necrosis. Positive culture and guinea-pig inoculation
		Cæcum, ascending and transverse	1	Operation specimen	Hyperplastic lesions with minimal caseation necrosis. Acid-fast bacilli present
Jordan and DeBakey	1954	Sigmoido-vesical	1	*a*. Operation specimen (Comer 1952)	Tubercle bacilli cultured from urine. Caseous tuberculosis of sigmoid
				b. Autopsy	T.B. plus carcinoma of sigmoid with recurrence of fistula

* References marked thus refer to articles which were not available to the author.

† A granuloma of the descending colon, presumably of tuberculous origin has been reported by Muir (1956)

with a history of bouts of umbilical and right iliac fossa pain for the past year. At first, attacks of colicky pain occurred once a week, but for the past three months pain had been frequently present, mainly felt during the night. The pain had no relation to food but was relieved by passage of flatus or fæces. There had never been any vomiting. Bowels had been irregular since onset of pain with periodic bouts of diarrhœa alternating with constipation. Blood had not been noticed in the stools. The patient complained of intermittent unproductive cough

and had lost weight. He was a miner working at the Kolar Gold Fields.

On Examination.—He was a thin young man in poor general condition. Conjunctivæ were pale. The cardio-vascular system was normal. A few moist sounds were heard in the right infra-clavicular region on deep inspiration. Apart from this, no other abnormality was found in the respiratory system. Examination of the abdomen revealed tenderness in the left hypochondrium and the right iliac fossa. A small mobile mass was also felt in the right iliac fossa. Rectal examination showed no abnormality. Hæmoglobin 9·0 g.; PPD reaction was positive. E.S.R., first hour 55, second hour 91. Fasting juice and stools were examined for acid-fast bacilli on several occasions with negative results. No cysts or vegetative amœbæ were found on examination of three fresh stool specimens. Chest radiograph : " Small infiltration in the right infraclavicular region—probably a minimal tuberculous infiltration." Barium enema (*Figs.* 78, 79): "Marked narrowing of distal transverse colon and cæcal regions. Probable tuberculosis of ileo-cæcal region with a second lesion in the transverse colon."

Fig. 78.—*Case* 2. Barium enema lesions in the ileo-cæcal area and transverse colon are shown.

Fig. 79.—*Case* 2. Barium enema. Air contrast radiography, lesion in distal part of transverse colon well shown.

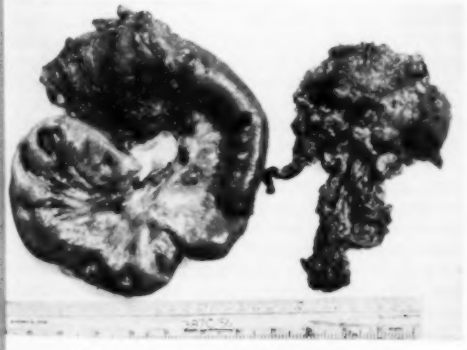

Fig. 80.—*Case* 2. Formalin fixed specimens.

Fig. 81.—*Case* 2. Formalin fixed specimens opened up.

Patient was given medical treatment including INAH 75 mg. t.d.s. and streptomycin 1 g. every 3 days for 6 weeks. Radiographs then showed a marked improvement in the right apical lesion and E.S.R. had fallen, first hour 25, second hour 55. However, during his stay in the ward, the patient complained of recurrent bouts of colicky abdominal pain. Twelve days prior to operation, he had a severe attack and examination showed moderate abdominal distension and visible peristalsis in the right lower quadrant with increased bowel sounds. This was relieved by institution of intravenous drip and continuous gastric suction for 24 hours.

AT OPERATION (Aug. 18, 1956 (D.M.H.)).—Laparotomy and (1) excision of distal half of transverse colon with end-to-end colo-colic anastomosis, and (2) excision of cæcum, portion of ascending colon, and terminal 3 ft. of ileum with end-to-end ileo-colostomy. Photographs of the formalin fixed specimen are shown (*Figs.* 80, 81).

Findings.—There were several strictures in the last 3 ft. of the terminal ileum with a nodular mass in the ileo-cæcal region. This area was separated by a length of normal colon from another narrowed segment about 2 in. long with nodular thickened walls in the distal part of the transverse colon. There was marked enlargement of the regional lymph-nodes in the mesentery of the small bowel, in the ileo-cæcal region, and in the area draining the distal transverse colon.

The patient made an uneventful recovery from this operation and was discharged on Aug. 29 with instructions to continue anti-tuberculous drugs for another 6 weeks.

FOLLOW-UP.—This patient was seen in April, 1957. He was in good health, had gained weight, and had returned to work. There had been no recurrence of symptoms.

HISTOLOGY.—Sections of cæcum and transverse colon show infiltration of muscle and serous coats with collections of epithelioid cells and giant cells. No caseation is seen in the bowel wall. The lymph-nodes examined show many tubercles and have small areas of caseation. Acid-fast bacilli were demonstrated on tissue staining.

SUMMARY.—Hyperplastic tuberculous bowel with lymph-node involvement.

Comment.—This patient was admitted with obstructive symptoms due to multiple cicatrizing lesions in the terminal ileum, cæcum, and distal transverse colon. One acute episode occurred in the ward twelve days pre-operatively. Follow-up has shown satisfactory post-operative progress. The histological features were similar to those found in the first case and the diagnosis of tuberculosis could only be made after a careful study of the lymph-glands.

DISCUSSION

A review of the records of this hospital during the last five years has shown one further case of true hyperplastic tuberculosis of the distal colon. The patient was a male aged 30. Laparotomy revealed a stricture of the sigmoid colon with subserous tubercles and thickening of the colon wall. Tubercles were also found over the small intestines in three areas and over the ileo-cæcal region. Excision of the sigmoid colon was carried out (Dr. H. S. Bhat). The specimen showed a picture of proliferative hyperplastic tuberculosis with gross and microscopic areas of caseation both in the colon wall and in the regional lymph-nodes. Acid-fast bacilli were demonstrated in these lesions.

There have been other cases of granuloma of this area which did not conform to the usual picture of regional colitis and were probably tuberculous. However, as definite caseation could not be demonstrated, and acid-fast bacilli were not seen, these cases have been excluded from this survey. There have also been cases of true hyperplastic tuberculosis of the proximal colon without involvement of the cæcal region. These also have been excluded.

The occurrence of these three cases of hyperplastic tuberculosis of the distal colon within a short space of time in this hospital must be viewed against the background of the frequency of similar ileo-cæcal lesions that are treated here. It appears that true ileo-cæcal hyperplastic tuberculosis is more common in India than in Western countries (Mistry and Pathak, 1954). However, full confirmation of this statement must await completion of the diagnosis in a large series in this country by acid-fast tissue staining, culture, and guinea-pig inoculation.

Criteria of Diagnosis of Hyperplastic Tuberculosis of the Colon.—It is recognized that many cases that used to be diagnosed as hyperplastic tuberculosis would now be shown to be cases of non-specific inflammatory granuloma such as Crohn's disease or regional colitis (Warren and Sommers, 1948; Wells, 1952; Neuman and Dockerty, 1954). Definite criteria must therefore be fulfilled before the diagnosis of tuberculosis is made in these large bowel granulomata. On pathological examination one of the main criteria used in this hospital is the presence of caseation, which must be searched for carefully and may be present in the regional glands whilst the bowel shows only non-specific inflammatory changes (Taylor, 1945).

The importance of the presence of true caseation in hyperplastic tuberculosis has been stressed (Hoon, Dockerty, and Pemberton, 1950; Wells; Neuman and Dockerty) since non-caseating tubercle-like nodular granulomas and areas of fibrinoid necrosis are frequently found in both regional colitis and regional ileitis. However, the presence of caseation cannot be stated to be an essential factor for the diagnosis of hyperplastic tuberculosis. Usually caseation is not marked in this disease (Taylor, Rappaport, Burgoyne, and Smetana, 1951), and Turell (1953), in a recent review, states that caseation is frequently absent. He emphasizes that the diagnosis should be based on acid-fast tissue stains and guinea-pig inoculation.

It is possible that productive tuberculous lesions without caseation may occur in patients with a low sensitivity and a high immunity to the disease, but caseation is probably caused by hypersensitivity (Florey, 1954), while the mononuclear cell and the epithelioid reaction together with some unidentified humeral factors are characteristic of the immune reaction (Lurie, 1950). However, this is a complicated question which cannot be gone into in detail here. Some observers have even suggested a causal relationship between hypersensitivity and the formation of non-caseating tubercle-like granulomas in regional enteritis (Tallroth, 1943; Rappaport and others, 1951), while Goddard (1947) has suggested that granulomas in general may represent a characteristic qualitative change in focal anaphylactic inflammation. Further work is needed to clarify this matter.

Caseation necrosis was not evident in the bowel wall in either of the cases presented here, but

definite though minimal areas were found in the lymph-glands. Also, in both cases, acid-fast bacilli were demonstrated. Unfortunately, culture and guinea-pig inoculation were not carried out, but even so, there is strong evidence for the tuberculous origin of these lesions.

TREATMENT

The treatment of these cases was along routine lines. The usefulness of adequate pre-operative treatment, when there is an associated lung lesion, is demonstrated in *Case* 2. Surgery had to be carried out earlier than originally intended in this case owing to recurrent bouts of acute intestinal obstruction. This complication has been noted in other cases receiving chemotherapy (Harris, 1952). These hyperplastic lesions rarely respond to chemotherapy or short-circuiting alone and resection is the treatment of choice (Misra and Pathak, 1954). Short-circuit operations which involve the formation of a blind loop or cul-de-sac should be avoided owing to the danger of megaloblastic anæmia and ileo-jejunal insufficiency with steatorrhœa supervening (Naish and Capper, 1953). At operation a thorough inspection of the whole small and large bowel should be carried out to exclude the presence of multiple lesions. When these are found multiple localized resections are indicated whenever possible. A closed method of anastomosis (Parker-Kerr technique) is of value if multiple colon resections and anastomoses need to be carried out in different parts of the abdomen, and this method was used in *Case* 2. Obstructive resection by the Paul-Mickulicz method may be used in poor-risk cases, as a wide resection of the lymph-glands is usually unnecessary.

CONCLUSIONS

There is no doubt that typical cases of regional colitis and regional enteritis are entities on their own. These two diseases may be related to each other (Wells, 1952), but they certainly should be differentiated from hyperplastic tuberculosis for many reasons including their peculiar course with a high-recurrence rate whatever treatment is used. However, in the border-line cases the possibility of a tuberculous origin must be borne in mind (Bockus and others, 1940). The presence of caseation is not essential for the diagnosis of hyperplastic tuberculosis and typical appearances may be obscured by secondary inflammation and lymphatic blockage. It is also wrong to label all epithelioid and giant-cell systems as being just a part of a non-specific foreign body reaction. Some of these systems may be part of a sarcoid type of lesion (MacFarlane, 1955) and in others tubercle bacilli may be demonstrated if sufficient care is taken. It is very important that a concentrated study of all intestinal granulomata should be undertaken and this should include a thorough search for tubercle bacilli by means of acid-fast tissue stains, culture, and guinea-pig inoculation. A careful follow-up of all cases is also essential in order to establish the pattern of the disease that is being dealt with. A study along these lines in areas of the world where tuberculosis is common and a broad spectrum of tissue reactions is regularly being seen, will help throw more light on this difficult problem of the intestinal granulomata.

SUMMARY

Two cases of hyperplastic tuberculosis of the distal colon are presented and the pathological features and treatment are discussed.

Acknowledgements.—I should like to thank Dr. E. Gault and Dr. G. Hadley for their help in the preparation of this paper, and for the pathology reports. My thanks are also due to Dr. I. B. Scudder, and Dr. D. E. Paterson for the radiology reports; to Mr. S. D. Sigamani for the photographs; to Mr. J. Williams for help with the references; and to Mrs. M. A. Furness for help with the clerical work.

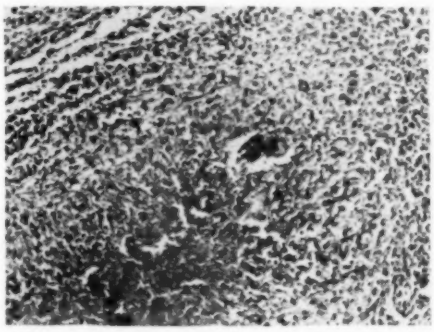

FIG. 82.—Area of caseation with epithelioid cells and giant cells situated in subserosa and outer layer of muscular coat of transverse colon at site of stricture. H. and E. (× 115.)

Addendum.—On July 28, 1957, after this article had been submitted for publication, an autopsy was performed in this hospital by Dr. Irwin Samuel, on a male patient, aged 33, who had been treated in the medical wards. The gastro-intestinal tract was normal apart from a localized hypertrophic stricture in the distal half of the transverse colon. The regional glands were enlarged at this site. On microscopy, many caseous granulomata were found both in the bowel wall and in the regional glands (*Fig.* 82). Non-caseous miliary granulomata were found in the liver and kidney, but not in the lungs. Unfortunately, tissue was not taken for culture or guinea-pig inoculation, and acid-fast bacilli have been repeatedly looked for with negative results. The diagnosis of hyperplastic tuberculosis in this case must therefore remain tentative, as other causes of caseous granulomata, such as infection with *Histoplasma*, *Brucella*, and *Coccidiodes* and *Cryptococcus* have not been excluded.

REFERENCES

ADAMS, R., and MILLER, W. H. (1946), *Surg. Clin. N. Amer.*, **26**, 656.

ANDERSON, J., and MUNRO, W. T. (1931), *Edinb. med. J.*, **38**, 159.

ARCHIBALD, E. W. (1920), *Canad. med. Ass. J.*, **10**, 804.

BANERJEA, B. N. (1950), *Indian J. Surg.*, **12**, 33.

BARGEN, J. A., COPELAND, M. M., and RANKIN, F. W. (1930), *Ann. Surg.*, **91**, 79.

BOCKUS, H. L. (1944), *Gastroenterology*, Vol. II, p. 209. Philadelphia and London: W. B. Saunders.

BOCKUS, H. L., TUMEN, H., and KORNBLOOM, K. (1940), *Ann. intern. Med.*, **13**, 1461.
CAIRD, J. B. (1921), *Edinb. med. J.*, **18**, 78.
COMER, J. V. (1952), *Ann. Surg.*, **136**, 901.
COOPER, F. G. (1932), *Amer. Rev. Tuberc.*, **25**, 108.
CULLEN, J. H. (1940), *Quart. Bull. Sea View Hosp.*, **5**, 143.
DAVIS, A. A. (1933), *Surg. Gynec. Obstet.*, **56**, 907.
DOWDLE, E. (1930), *Ann. Surg.*, **91**, 786.
FLOREY, H. (1954), *Lectures on General Pathology*. London: Lloyd-Luke.
FRIMODT-MOLLER, J. (1943), *Indian med. Gaz.*, **78**, 505.
GODDARD, J. W. (1947), *Amer. J. Path.*, **23**, 943.
HARRIS, W. C. (1952), *Tubercle*, **33**, 50.
HICKINBOTHAM, P. (1950), *Brit. J. Surg.*, **37**, 360.
HOON, J. R., DOCKERTY, M. B., and PEMBERTON, J. deJ. (1950), *Int. Abstr. Surg.*, **91**, 417.
JORDAN, G. L., and DEBAKEY, M. E. (1954), *Arch. Surg., Chicago*, **69**, 688.
KORNBLUM, S. S., ZALE, C., and ARONSON, W. (1948), *Amer. J. Surg.*, **75**, 498.
LOCKHART MUMMERY, P. (1923), *Diseases of the Rectum and Colon and their Surgical Treatment*. New York: William Wood.
LURIE, M. B. (1950), *Amer. J. Med.*, **9**, 591.
MACFARLANE, D. A. (1955), *Brit. J. Surg.*, **42**, 639.
MAILER, R. (1927), *Amer. J. Surg.*, **2**, 142.
MAYO, W. J. (1899), *N.Y. med. J.*, **70**, 253.
MILLER, J. K. (1936), *J. Amer. med. Ass.*, **107**, 1560.
MISRA, S. C., and PATHAK, S. S. (1954), *J. Indian med. Ass.*, **23**, 240.
MUIR, E. G. (1956), *Proc. R. Soc. med.*, **49**, 473.
NAISH, J., and CAPPER, W. M. (1953), *Lancet*, **2**, 597.
NEUMAN, H. W., and DOCKERTY, M. B. (1954), *Surg. Gynec. Obstet.*, **99**, 572.
RANDALL, K. J., and SPALDING, J. E. (1946), *Brit. J. Surg.*, **33**, 372.
RANKIN, F. W., and MAJOR, S. G. (1932), *Surg. Gynec. Obstet.*, **55**, 494.
RAPPAPORT, H., BURGOYNE, F. H., and SMETANA, H. F. (1951), *Milit. Surg.*, **109**, 463.
TALLROTH, A. (1943), *Acta. chir. scand.*, **88**, 407.
TAYLOR, A. W. (1945), *Brit. J. Surg.*, **33**, 178.
TURELL, R. (1953), *Int. Abstr. Surg.*, **96**, 417.
WARREN, S., and SOMMERS, S. C. (1948), *Amer. J. Path.*, **24**, 475.
WELLS, C. (1952), *Ann. R. Coll. Surg. Engl.*, **11**, 105.
YEOMANS, F. C. (1929), *Proctology, a Treatise on the Malformations, Injuries and Diseases of the Rectum, Anus and Pelvic Colon*, p. 334. New York: Appleton.

HEPATIC JAUNDICE AFTER BLOOD TRANSFUSION IN INJURED AND BURNED SUBJECTS

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THIS communication describes the development of jaundice in some injured or burned patients after transfusion with stored blood and within a few days of the accident or subsequent operation. Many cases were referred to the laboratory as possible hæmolytic transfusion reactions, but serological and other studies failed to reveal any evidence of blood incompatibility or of intravascular hæmolysis. Biochemical investigations showed that the serum-jaundice was hepatic in origin since it was associated with a positive direct van den Bergh reaction, bilirubinuria (biliuria), urobilinuria, and often other evidence of liver impairment, such as a raised serum-alkaline phosphatase level and sometimes increased thymol and zinc-sulphate serum-turbidity reactions. Clinically the condition was generally mild and the jaundice disappeared within a week, but occasionally it was more severe and it may have contributed to the death of a burned patient. There was no clinical or laboratory indication of a *pre-existing* hepatic dysfunction. Jaundice was probably induced by a combination of two circumstances: (1) A temporary hepatic impairment, and (2) The acute loading of the circulation with bilirubin formed through the extravascular destruction of the non-viable proportion of red cells in stored blood. The temporary liver dysfunction which followed injury, burning, subsequent operations, and anæsthesia or a combination of these, probably resulted from a lowered circulation through the liver, possibly aided by hepato-toxic, infective or other complications in some patients. In other words, the blood transfusion appeared to have acted as a bilirubin-loading test of liver function, and since this was acutely disturbed, jaundice with biliuria appeared.

THE PATIENTS

Studies were made on 16 patients during 1952–6, 12 injured and 4 burned subjects (*Table I*). Six other patients have been excluded from the analysis because there was evidence of coexisting hepato-biliary complication or disease. In them jaundice was either precipitated or acutely deepened by blood transfusion.

Injured Subjects.—All the twelve patients were adults aged 32–80 years and 8 were males. In 4 the injuries were confined to a pertrochanteric or intracapsular fracture of the femoral neck and a Neufeldt nail-plate operation or a Smith-Petersen pinning was carried out under general anæsthesia. The other eight had severe injuries. One had abdominal injuries and laparotomy revealed a ruptured bowel (*Case* 8). *Case* 2 suffered fractures of the tibia, ankle, and spine; *Case* 4 had a fractured pelvis and a ruptured urethra which required emergency surgery; *Case* 5 sustained pelvic and rib fractures and a ruptured kidney, and a laparotomy was performed 2 days later; *Case* 6 suffered a severe crushing of the thigh which had to be amputated a week later; *Case* 7 had a fractured shaft of the femur which was treated by traction; *Case* 11 had a fractured pelvis, a compound fracture of the femur and severe leg injuries which necessitated an emergency mid-thigh amputation; and *Case* 12 sustained a fractured pelvis, tibia, and fibula. This patient died 19 days after injury, and autopsy revealed coronary artery occlusion, a ruptured bladder, and extravasation of urine.

Burned Subjects.—Three of the four patients were male adults 30–47 years old and the other was a girl of 8 years. They were extensively burned and 25

per cent to 60 per cent of the body area was involved. One patient (*Case* 15) fell into a vat of hot soda, whilst the others were burned by flame after various accidents. During the first 24 to 72 hours (shock period) 3 were transfused with 4·7 to 20 litres of reconstituted dried plasma, the other with 1·3 litres of dextran, and 3 were also transfused with blood. Each patient was subsequently skin-grafted under general anæsthesia usually 2–4 weeks after burning and blood transfusions were always given. In 2 patients, however, jaundice occurred before the first operation.

Table I.—THE SIXTEEN CASES OF JAUNDICE AFTER TRANSFUSION WITH STORED BLOOD

CASE NO., SEX AND AGE (Years)	INJURIES OR BURNS (Percentage Body Area)	OPERATIONS AND OTHER DETAILS	BLOOD TRANSFUSION (No. Pint Bottles)	JAUNDICE (Onset, Biliuria, etc.)
Case 1 M. 35	Pertrochanteric fracture of femur	1. Neufeldt nailing, day 1* 2. Drainage of infected operation wound, day 15. (Culture—Group A *streptococcus*)	1. 3 during 1st operation 2. 3 during 2nd operation	Biliuria day after 2nd operation and transfusion. Serum bilirubin 2·0 mg. per cent 2 days later. No clinical jaundice
Case 2 M. 38	Fracture of tibia, ankle, spine	No operation	5 on day 0	Clinical jaundice, nausea and pyrexia day 4. Biliuria. Serum bilirubin 4·9 mg. per cent
Case 3 M. 78	Pertrochanteric fracture of femur	Neufeldt nailing, day 3	3 on day 3	Clinical jaundice 4 days after operation and transfusion. Vomited. Biliuria. Serum bilirubin 4·5 mg. per cent
Case 4 M. 38	Fractured pelvis, ruptured urethra	Cystotomy and urethral repair day 0	1. 5 day 0 and 1 2. 2 day 4 3. day 7	Clinical jaundice day after 2nd transfusion. Clinical condition poor. Biliuria + +. Serum bilirubin 7·6 mg. per cent
Case 5 M. 32	Fracture of ribs, pelvis, ruptured kidney	Laparotomy, day 2. (B.P. 80–60/ several hours on day 0)	8 days 0 and 1	Clinical jaundice day 4. Biliuria + +. Serum bilirubin rose from 0·7 mg. on day 0 to 6·9 mg. per cent day 5
Case 6 M. 55	Crushed thigh	1. Exploration of thigh, day 0 2. Amputation, day 7	1. 7 day 0 2. 2 day 5 3. 5 day 7 4. 2 day 16	Deeply jaundiced day after amputation and 3rd transfusion. Pyrexia. Biliuria + +. Serum bilirubin 8·5 mg. per cent. Jaundice lasted a few days but jaundice and biliuria reappeared after transfusion 4
Case 7 F. 80	Fracture of shaft of femur	No operation Hypochromic anæmia Paroxysmal tachycardia	3 day 0	Clinical jaundice day 3. Tender over liver. Biliuria. Serum bilirubin 3·3 mg. per cent
Case 8 M. 56	Ruptured bowel, torn mesentery	1. Colostomy, exteriorization of bowel, day 0 2. Repair burst wound, day 5	1. 9 day 0 2. 2 during 2nd operation	Serum jaundice, biliuria day after 2nd operation and transfusion. Serum bilirubin 3·9 mg. per cent
Case 9 F. 54	Pertrochanteric fracture of femur	Neufeldt nailing, day 1 Septic hæmatoma of operation wound (Culture—*Staph. aureus*)	1. 3 during 1st operation 2. 3 day 14	Slight jaundice day 7. Looked ill, pyrexia, tender over liver. Serum bilirubin 2·2 mg. per cent. Slight biliuria
Case 10 F. 74	Fracture of neck of femur	Smith-Peterson nailing, day 1 Diabetes mellitus, insulin 15 units b.d.	2 during operation	Clinical jaundice day 5. Biliuria + +. Serum bilirubin rose from 0·7 mg. per cent on day 0 to 5·8 mg. per cent day 5
Case 11 M. 45	Compound fracture of femur, severe leg injury, fracture of pelvis	Mid-thigh amputation, day 0	1. 13 days 0 and 1 2. 2 of packed cells day 6	Slight jaundice day 5 preceded by pyrexia, tachycardia, vomiting. Biliuria. Serum bilirubin 7·6 mg. per cent. Jaundice deepened by 2nd transfusion and lasted a few days
Case 12 F. 80	Fracture of pelvis, perforated bladder, fracture of tibia, fibula	B.P. fell to 90/50 day of injury	1. 5 day 0 2. 3 day 7	Jaundiced day 8, day after 2nd transfusion. Biliuria. Serum bilirubin 8·8 mg. per cent. 5 days later 7·0 mg. per cent. Became drowsy, blood-urea 133 mg. per cent day 13, died day 19. Autopsy—coronary occlusion
Case 13 F. 8	28 per cent burns	4·7 litres plasma in shock period Grafting operation, day 18	1. 2 day 7 2. 2 day 17 3. 2 day 18 Transfusions 3 and 5 weeks later	Icterus of conjunctivæ 6 hours after operation day 18. Biliuria + +. Serum bilirubin 2 mg. per cent
Case 14 M. 33	30 per cent burns	10 litres plasma in shock period	2 day 0 and subsequent transfusions	Serum jaundice (bilirubin 3·8 mg. per cent) day 4. Slight biliuria
Case 15 M. 30	60 per cent burns (hot soda)	20 litres plasma in shock period	4 days 0–2 7 days 13–15 5 day 21 and subsequent transfusions	Slight clinical jaundice day 8. Biliuria +. Serum bilirubin 3·9 mg. per cent. Trace biliuria after transfusion day 21
Case 16 M. 47	25 per cent burns	1·3 litres dextran (no plasma) in shock period Grafting operation, day 35	1. 6 day 0 2. 4 day 32 3. 5 day 35	Clinical jaundice day after operation and transfusions on day 35. Biliuria + +, but serum bilirubin only 1·6 mg. per cent. Hyperglycæmia and glycosuria. Comatose day 41. Died day 44

* Day 0—day of burning or injury; day 1, 2, 3, etc.—first, second, third, etc., day after burning or injury.

One patient (*Case* 16) died. He succumbed 44 days after burning, 8 days after the onset of jaundice, and was jaundiced at autopsy. The liver was enlarged and swollen, the histology showed swollen parenchymal cells and compressed sinusoids, but the main lethal findings were bronchopneumonia, fibrinous pericarditis, and toxic myocarditis. Nevertheless, hepatic jaundice probably contributed to his death.

TRANSFUSED BLOOD AND LABORATORY TESTS

All the patients were transfused and blood of the patients' ABO group and Rhesus (D) type was nearly always given after careful cross-matching of the patients' serum against suspensions of the donors' cells both in saline and albumin solution at 37° C. Cross-matching was supplemented by indirect anti-human globulin (Coombs') tests when previous transfusions had been given. Three of the patients who required emergency transfusion on admission for acute hæmorrhagic shock (*Cases* 2, 8, and 11) were given 1 or 2 bottles of initially un-cross-matched Group O, Rh negative (D negative) blood whilst subsequent bottles were of the homologous group and type.

The bottles of blood were stored at 4° C. (±1° C.) in a refrigerator specially designed for a hospital blood-bank (Sevitt, 1953). Every bottle was transfused within 21 days of its being bled from the donor; 56 per cent of them were less than two weeks old, and 24 per cent less than one week old. Blood-bank organization included visible inspection of each bottle by a trained technician and in none was there evidence of hæmolysis or other abnormality. Only one bottle of blood per patient was given out at a time and each was transfused within an hour, often within minutes of leaving the refrigerator.

The appearance of jaundice after the transfusion raised the possibility of blood incompatibility and hæmolytic transfusion reaction in 10 patients and special laboratory investigations were carried out. The patient's blood was regrouped and Rhesus-typed, the donors' cells were re-cross-matched with the pre-transfusion serum, indirect antiglobulin and other tests for incomplete and irregular antibodies were made, and direct antiglobulin tests were performed on the patient's post-transfusion cells. There was no evidence of blood-group incompatibility, sensitization of the circulating recipient, or transfused cells or of irregular antibodies. The post-transfusion serum was examined for hæmoglobin and methæmalbumin (Schumm's test) and the urine for hæmoglobinuria (13 patients), but these investigations failed to show intravascular hæmolysis. Furthermore, biliuria and the direct serum van den Bergh reaction were evidence against hæmolytic reactions.

Subsequent serological investigations in 13 patients failed to reveal the development of irregular or abnormal antibodies. In 5 patients the question was studied in sera removed 10–14 days after the first transfusion by tests involving a panel of Group O cells of known types (Rhesus, Kell, P, MNS, Lutheran). Moreover, in 11 subjects one or more series of subsequent cross-matches for transfusion against 2 to 9 samples of homologous (ABO and Rhesus D) donor cell suspensions were carried out with sera removed from the patients 6 to 32 days after the first transfusion and subsequently in 6 cases. Neither by these saline or albumin cross-matches nor by indirect antiglobulin tests were abnormal antibodies detected.

One of the criteria for detecting destruction of red cells after transfusion is a failure of the peripheral hæmoglobin level to rise by an expected value per volume transfused and by a subsequent fall in the hæmoglobin value. These tests which indicate changes in the red-cell mass were of limited value for this purpose in the present series of cases because acute oligæmia, continued bleeding, subsequent hæmodilution, and operative losses complicated the matter. For example, transfusion of blood insufficient to correct post-traumatic oligæmia will be followed by an apparently inadequate rise or even by a fall in the peripheral hæmoglobin value because of the subsequent hæmodilution and increase of plasma volume. Serial hæmoglobin estimates after one or more transfusions were studied in 14 patients. In none of them did a fall occur which could not be explained by the initial injury or operative losses. More significantly when the hæmoglobin level was restored to normal or near normal by transfusion a week or more after injury (that is, when the blood-volume was presumably about normal) it never fell during the following week or two even though jaundice developed after the transfusion. For example, in *Case* 12 the hæmoglobin value which fell from 15 g. per 100 ml. on the day of injury to 10·2 g. per cent 7 days later when 3 bottles of blood were transfused, rose to 13·2 g. the next day when jaundice appeared. During the subsequent 10 days the hæmoglobin values fluctuated between 12·6 and 14·4 g. per cent. Similarly, in *Case* 6 amputation of the thigh and transfuson of 5 bottles of blood on the seventh day after injury was followed by jaundice and hæmoglobin levels of 11·7, 11·7, 12·9, and 14·4 g. per cent 1, 3, 6, and 10 days later.

JAUNDICE

Jaundice of the skin and conjunctivæ developed in 13 patients, the depth of colour was slight in two of them but it was definite in the others and quite deep in a few. In the other three patients (*Cases* 1, 8, and 14) jaundice was subclinical, staining of the skin was not observed, but the serum was yellow and biliuria was present.

Jaundice was preceded or associated with other signs and symptoms in 7 or 8 patients, particularly pyrexia, nausea or vomiting, and tenderness over the liver area.

The jaundice lasted a few days and appeared to have no prognostic or clinical significance except in one burned patient in whom it may have contributed to death (*see* above). Jaundice and biliuria recurred or deepened in a few patients after a subsequent transfusion.

Illustrative examples.—

Case 5.—A man of 32 years fell off a motor cycle and was admitted to hospital half an hour later. He was pale and appeared shocked (B.P. 110/75, pulse 100 per minute) and he complained of dyspnœa and pain over the left chest and hip. A large hæmatoma in the left loin and hæmaturia were present. Diagnosis was made of fractured ribs (9–12), fractured pelvis, and a ruptured kidney. Intravenous pyelography was normal and it was decided

to try and save the kidney. Eight bottles of blood were transfused over 18 hours, but the blood-pressure fell to 80/50 for several hours. Next day the patient's condition worsened, he was vomiting, and his abdomen became distended. Exploratory laparotomy 2 days after injury showed only a large retroperitoneal hæmatoma. Post-operative gastric suction was given, 2 days later he was feeling much better but he became deeply jaundiced. This had disappeared a week later. Biochemical investigations

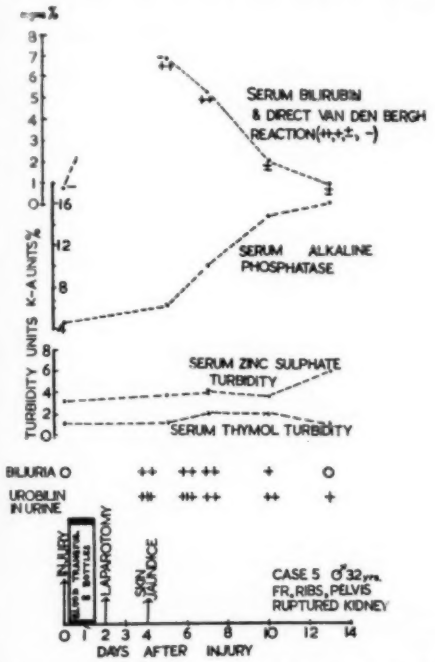

FIG. 83.—Serum bilirubin values and direct van den Bergh reactions in the 16 patients at various times after the last transfusion of blood. The interrupted horizontal lines indicate the normal range of serum bilirubin.

(*Fig.* 83) showed a considerable bilirubinuria for 6-9 days. The serum bilirubin level which was 0·7 mg. per cent on the day of injury rose to 6·9 mg. 5 days later (day 5) and fell to 5·3, 2·1, 1·0 mg. per cent respectively on days 7, 10, and 13. The direct serum van den Bergh test was strongly positive, urobilinuria was considerable (Ehrlich's reaction for urobilinogen was positive in a urine dilution of 1 in 60), the level of serum alkaline phosphatase rose progressively from 4·3 King-Armstrong units on day 0, to 6·2, 10·3, 14·6, and 15·4 units during the next 10 days, the one-stage plasma prothrombin test showed a 30-40 per cent reduction of prothrombin activity, and 10 days after injury the zinc sulphate serum turbidity test reached an abnormal level of 6 units. Thus the biochemical findings indicated liver impairment and hepatic jaundice.

Case 6.—The left thigh of this 55-year-old male was badly crushed and he was admitted to hospital 1½ hours later. The thigh was not very swollen but sensation was diminished in the foot. Blood-pressure was 137/75. An exploratory operation under general anæsthesia was performed 4 hours later and 7 bottles of Group A, Rh-positive blood were transfused (patient Group A, Rh-positive). The damaged muscle was excised and the femoral artery was seen to be arteriosclerotic and damaged. Post-operatively, penicillin and aureomycin therapy were instituted and ice-bags were applied around the whole limb. His general condition remained fair but 4 days later the left foot was cold, blue, and lifeless. Patient was pyrexial, some diarrhœa and vomiting occurred, but ceased when aureomycin was discontinued. Seven days after injury a mid-thigh amputation was carried out under general anæsthesia and 5 bottles of homologous blood were transfused. Next day he was deeply jaundiced, the serum bilirubin level was 8·5 mg. per cent, the direct serum van den Bergh reaction was strongly positive, and there was considerable biliuria and urobilinuria. The biliuria lasted a few days and 3 days after operation the skin jaundice was fading. Jaundice and biliuria reappeared temporarily after a transfusion of 2 bottles of blood 16 days after injury, but 5 days later the serum bilirubin had fallen to 0·8 mg. per cent. Fæcal urobilinogen was greatly increased (435 mg. per 100 g. fæces).

Case 13.—This 8-year-old girl sustained full thickness skin-loss burns on both thighs, buttocks, and hands (28 per cent of the body area). During the first 48 hours intravenous plasma (4·7 litres) was given, a phase of deep hæmoglobinuria occurred, but the urine output was maintained. The burns were then dressed and penicillin cream was applied. Blood transfusions, each of 2 bottles, were given 7 and 17 days after burning. On the eighteenth day a skin-grafting operation was performed under general anæsthesia, and 2 bottles of blood were transfused. All transfusions were with Group O, Rh-positive blood, the patient being the same. Six hours later the conjunctivæ were icteric. Biluria was found and lasted 3 days and urobilinuria was considerable. The serum bilirubin level on the day after the operation was only 2 mg. per cent (weak positive direct van den Bergh reaction) and fell to 0·7 mg. per cent 2 days later. The serum alkaline phosphatase rose from 7·5 units the day after operation to 13 units 2 days later, and the serum zinc-sulphate turbidity varied from 6 to 7 units.

BIOCHEMICAL FINDINGS

Serum jaundice was associated with a direct van den Bergh reaction, biliuria, and urobilinuria. There was often a slight or moderate increase in the serum alkaline phosphatase values and sometimes an increased turbidity in the serum thymol or zinc-sulphate tests. The results indicated that the jaundice was hepatic in origin and was not the result of hæmolysis or biliary obstruction.

Serum Bilirubin.—In *Fig.* 84 the serum levels are plotted against time in days after the last transfusion. Pre-transfusion samples of serum from 4 patients were available and showed normal bilirubin values. The bilirubin level remained elevated for days after the transfusion and then fell to normal limits some days later. The maximum values determined ranged from 1·6 to 8·8 mg. per cent and in 12 patients were greater than 3·3 mg. per cent. The duration of serum jaundice was longer in those with the higher maximum values and vice versa; it varied from 2 to 12 days, but usually lasted about a week.

Direct van den Bergh Reaction.—In all patients except one (*Case* 7) the direct serum van den Bergh test was positive indicating that the jaundice was not hæmolytic in origin. The reaction was strongly positive (++) when the serum bilirubin level was above 4 or 5 mg. per cent and was or became, less strong with lower values. When the level was below about 2 mg. per cent weak (±) or sometimes negative reactions were found.

Biliuria (bilirubinuria).—Biliuria was found in all patients including *Case* 7 (*see p.* 71). Initially Fouchet's test was strongly positive and often Smith's iodine test as well. The strength of the reaction was generally higher with the higher serum bilirubin levels, but biliuria was usually detected even when the serum concentration was between 1 and 2 mg. per cent. In most cases it was weak at these serum levels but in *Cases* 13 and 16 Fouchet's test was strongly positive when the serum bilirubins were only 2 and 1·6 mg. per cent respectively.

Urobilinuria and Urobilinogenuria.—Excessive urobilinuria (Schlesinger's zinc acetate test) was found during the biliuria in 15 patients and in 8 of them very strong reactions were obtained. Considerable urobilinogen (Ehrlich's aldehyde test) was also present and in nearly all subjects the urine gave a positive reaction at a dilution of 1 in 5 or more (1/20 to 1/60 in several.)

Excessive urobilinuria is consistent with, but does not necessarily indicate liver dysfunction, since it is a common finding in patients with excessive blood destruction and in the writer's experience occurs in 40–60 per cent of patients after transfusion of blood.

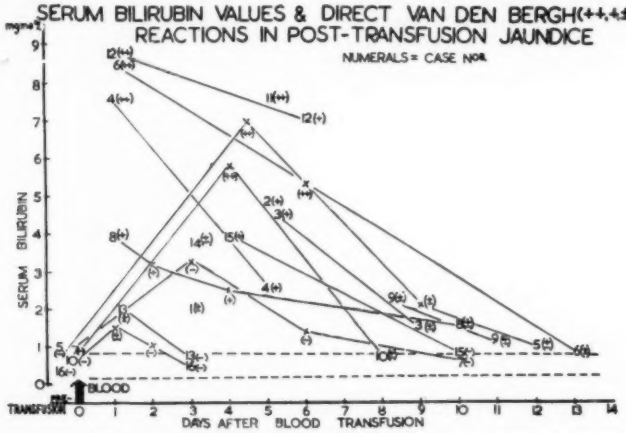

FIG. 84.—*Case* 5. Serum and urinary investigations relevant to jaundice on various days after injury.

Table II.—ASSESSMENT OF AETIOLOGICAL FACTORS IN HEPATIC JAUNDICE FOLLOWING BLOOD TRANSFUSION

	TRAUMA AND BLOOD TRANSFUSION	TRAUMA, OPERATION, ANÆSTHESIA, AND BLOOD TRANSFUSION	BURNS AND BLOOD TRANSFUSION	BURNS, OPERATION, ANÆSTHESIA, AND BLOOD TRANSFUSION
No. of Cases	3	9	2	2

Serum Alkaline Phosphatase.—Single or repeated estimations were carried out in 12 patients. In 6 of them one or more estimations were higher than the normal range (3–13 King-Armstrong units) and the abnormal values ranged from 14 to 23 units. In 3 subjects (*Cases* 5, 8, and 16) serial observations showed a rapid or progressive rise during the first 2–10 days. These observations are consistent with hepatic impairment. A moderate increase in the alkaline phosphatase level is also found in patients with fractures, but in *Cases* 8 and 16 bony injuries were absent.

Thymol and Zinc-sulphate Serum Turbidity Tests.—Single and repeated serum-turbidity tests of 'liver function' were made in 15 patients. Slightly raised thymol-turbidities (3–5 units) were found in 4 cases, raised zinc-sulphate values (5–7 units) in 4 patients, and one or both tests were abnormal in 7 subjects (47 per cent). This incidence may have been higher if serial tests had been performed on more patients.

AETIOLOGICAL FACTORS

The development of jaundice was closely related to the administration of blood, but other factors must also have been involved since jaundice is uncommon after blood transfusion. Hepatogenic donor plasma or blood was not responsible because the jaundice generally occurred within a few days. The effects of injury or burning, or of operation and anæsthesia, or a combination of these were probably responsible.

A summarized assessment of the probable aetiological factors is given in *Table II*; 3 of the 12 injured patients became jaundiced after blood transfusion and the early sequelæ of injury, and 9 after blood transfusion and the results of injury, operation, and anæsthesia; 2 of the burned subjects became jaundiced after blood transfusion and the early effects of burning and the other 2 after blood transfusion, the later effects of deep burns (e.g., sloughing, exudation, and infection) as well as operation and anæsthesia.

The multiplicity of factors does not exclude other possible contributory causes in individual patients, such as the effects on the liver of cardiac embarrassment from paroxysmal tachycardia in *Case* 7, and the possible hepatotoxic effects of infected wounds (*Cases* 1 and 9) or burns (*Cases* 13 and 16).

Blood Transfusion.—Jaundice or biliuria or both always developed within a few days of one or other blood transfusion. The periods are given in *Table III*, which shows that 7 patients became

jaundiced within 24 hours, 10 within 3 days, and all within 6 days of the last transfusion. The clinical impression was that of a *propter hoc* as well as a *post hoc* connexion between the giving of blood and the onset of jaundice. Jaundice appeared after the first transfusion in 9 patients (in 5 it was the only transfusion given) and the volume of blood ranged from 2 to 13 pint bottles (in 6 subjects, 2 to 4 bottles). Jaundice occurred after the second transfusion in 5 others and after the third or subsequent transfusion in the remaining 2. The transfused volume varied from 2 to 5 pints.

Table III.—Intervals from Injury to the Onset of Jaundice and/or Biliuria

Interval in Days	No. of Cases in which Jaundice or Biliuria started at stated Intervals after:—		
	1 Injury or Burning	2 Operation and Anæsthesia	3 Blood Transfusion
1	0	5	7
2–3	1	1	3
4–6	7	5	6
7–8	5	0	0
>16	3	0	0

Jaundice and/or biliuria reappeared or deepened after a subsequent transfusion in *Cases* 6, 11, and 15. For example, the early slight jaundice in *Case* 11 became more definite after the administration of two bottles of packed red cells.

Injury, Burning, Operation (and Anæsthesia) and other Factors.—The periods from trauma or burning to the onset of jaundice or biliuria are given in *Table III*. The patients may be divided into two groups: (1) Those developing jaundice or biliuria within 8 days of the accident (13 patients): and (2) Those in whom it was delayed for 16 days or longer (3 patients). Even in the first group the intervals are generally longer than those between transfusion and jaundice or operation and jaundice; only 1 subject was jaundiced within 3 days of the accident and 7 within 4 to 6 days. In the second group jaundice cannot be attributed to the early effects of injury.

Five patients (3 injured, 2 burned) became jaundiced 4 or 8 days after injury and before any operation was performed. In them the severity of the injuries or the extent of burning suggested that the accident had predisposed to jaundice.

In the other 11 subjects (*Table III*) jaundice or biliuria appeared within a few days of operation under general anæsthesia, in 5 within 24 hours, and 2 to 6 days later in the others.

Consider the 8 subjects with severe injuries. Blood was given within an hour or two of admission to hospital and 4 patients had emergency operations. Five were jaundiced 3 to 5 days after injury, two others became jaundiced after operations and transfusions on the sixth and 8th days, and the other after the second transfusion on the seventh day. The 4 patients with less severe injuries (fractured necks of femur) had operations and transfusions 1 day or 3 days after injury; 3 of them were jaundiced 4 to 6 days later, whilst biliuria in the other appeared after a subsequent operation.

Two burned patients became jaundiced after skin-grafting operations and blood transfusions.

PATHOGENESIS

Hepatic jaundice after blood transfusion is an uncommon condition and it develops only in a small proportion of injured or burned subjects. It also occasionally occurs in patients undergoing operation without transfusion. The manner in which the jaundice occurs is not known with certainty, but the available evidence indicates that (1) predisposing and (2) precipitating mechanisms are involved. The former appears to be an acute impairment of liver function following injury, burning, operation and anæsthesia, singly or often in combination, whilst the latter is probably an acute loading of the bloodstream with bilirubin derived from the extravascular destruction of a portion of the transfused stored blood. In individual cases supplementary influences may contribute to liver dysfunction, such as the effects of cardiac embarrassment on the liver circulation or the possible hepatotoxic effects of wound infection. Further, the loading of the circulation with bilirubin may be aided by post-traumatic extravasation of blood, and in burned patients by the early and acute destruction of some of the patients' red cells (*see* Sevitt, 1957).

Acute Liver Impairment.—The splanchnic-liver circulation is considerably reduced after burning (Abell and Page, 1943; Dobson and Warner, 1954) and a fall probably occurs in injured subjects. This is probably related to the lowered cardiac output following injury, burning, or hæmorrhage and largely due to oligæmia (Richards, 1943–4; Lauson, Bradley and Cournand 1944), and is part of the regional reduction in blood-flow which affects the skin, kidneys, and other organs. The major hepatic circulation is venous and a significant reduction in the flow is therefore likely to produce oxygen lack at an early stage. Engel (1945) found that in animals subjected to acute hæmorrhage the oxygen saturation of the hepatic venous blood decreased before a fall occurred in the oxygen content of portal venous blood, the plasma amino-nitrogen rose, the oxygen consumption of liver slices measured *in vitro* was reduced, and he concluded that there was a rapid onset of hepatic anoxia and impairment of liver function.

The liver-splanchnic circulation is also reduced by about 30 per cent in patients under general anæsthesia (Shackman, Graber, and Melrose, 1953) and a further reduction occurs during the course of major surgery (Graber, 1957). The oxygen content of the hepatic venous blood was found to be normal and therefore the oxygen consumption of the liver and splanchnic tissues was reduced. This may be due to or give rise to impairment of liver cell function. The reduced liver circulation, which must largely result from splanchnic-vasoconstriction, is part of a major circulatory readjustment to anæsthesia because the blood-flow through the skin and muscles is greatly increased and receives almost half the cardiac output (Shackman, Graber, and Melrose, 1952).

Evidence of liver dysfunction is found in many injured patients (Scott, Olney, and Howard, 1955) and in subjects after surgical operations. The Quick hippuric acid synthesis test remained low

for days in normal subjects after appendicectomy or hernioplasty (Boyce and McFetridge, 1938) and the degree of bromsulphthalein retention was increased in many patients after extra-abdominal (Tagnon, Robbins, and Nichols, 1948) or abdominal operations (Zamchek, Chalmers, and Davidson, 1949). Zamchek and his colleagues also found a raised post-operative serum-bilirubin level in some patients; and liver biopsies removed before abdominal closure showed subcapsular or centrilobular collections of leucocytes and necrosis of some liver cells.

It may be concluded that some degree of liver dysfunction is a common event after traumatic oligæmia, extensive burning, general anæsthesia, and major surgical procedures. Further, the degree and duration of impairment is likely to be increased when an injury or burn is followed by one or more operations under general anæsthesia.

Bilirubin-loading of the Circulation.—Scott, Olney, and Howard found that the serum bilirubin level of many battle casualties rose after blood transfusion and sometimes remained elevated for days. There was additional evidence of liver impairment, particularly in the patients with persistent bilirubinæmia, namely, abnormal retention of bromsulphthalein, increased urinary excretion of urobilinogen, some loss of plasma prothrombin activity, and a raised serum cephalin flocculation. They concluded that the plasma jaundice reflected some degree of liver dysfunction associated with a load of bilirubin derived from the transfusion. Unlike the present cases the raised serum bilirubin level was not associated with a direct van den Bergh reaction and neither bilirubinuria nor clinical jaundice was reported.

Blood stored in acid-citrate dextrose solution at about 4° C. becomes unsuitable for transfusion after about three weeks because a high proportion of the preserved red cells have become non-viable. Even when stored for a shorter period cells disappear from the blood-stream within a few hours of transfusion. Mollison (1951) calculated that 8 per cent and 24 per cent of red cells stored for 14 and 28 days respectively disappeared from the circulation within 24 hours of transfusion and mostly in the first few hours. Assuming that the average non-viable proportion is about 10 per cent, then after a transfusion of 1 litre of blood the red cells in about 100 ml. (containing say 12 g. hæmoglobin) are rapidly removed by the reticulo-endothelial system where they are broken down to bilirubin and iron-containing pigments. The bilirubin liberated may be sufficient to produce jaundice if hepatic function is disturbed. The *relative* molecular weights of hæmoglobin (16,700) and bilirubin (584) indicate that the breakdown of 12 g. hæmoglobin gives rise to about 420 mg. bilirubin. Assuming a plasma volume of 3 litres this could raise the bilirubin level of the plasma by 14 mg. per 100 ml. if all the bilirubin were liberated at the same time and none were excreted by the liver or passed into the extracellular fluid; and even if it rapidly diffused into the extracellular fluid the additional plasma level would be about 3 mg. per cent—sufficient to stain the skin. In normal subjects excess plasma bilirubin is rapidly removed by the liver, and in the writer's experience the plasma bilirubin level often rises to 1 or 1·5 mg. per cent within a few hours of transfusion, but falls to normal in about twenty-four hours, presumably because liver function is sufficient to excrete the extra bilirubin into the bile. On the other hand, if the intra-hepatic excretion of bilirubin is handicapped, much of the bilirubin will acquire a positive van den Bergh reaction, enough may accumulate in the blood-stream and extracellular fluid to produce jaundice and to overflow into the urine. Presumably this is what happened to the sixteen patients described. Moreover in many of the injured subjects the bilirubin loading was aided by the post-traumatic extravasation of blood, and in 2 burned subjects this was additional to bilirubin formed after early destruction of some of the patient's red cells.

SUMMARY

The development of jaundice in 12 injured and 4 burned subjects soon after transfusion with stored blood is described. In 9 injured and 2 burned patients the jaundice was also related to operation and general anæsthesia. The jaundice, which generally disappeared within a week, was hepatic in origin because it was associated with a direct serum van den Bergh reaction, bilirubinuria, urobilinuria, often a raised serum alkaline phosphatase level, and sometimes increased thymol and zinc-sulphate turbidity reactions. There was no evidence of blood incompatibility or of intravascular hæmolysis. The evidence indicates that the jaundice resulted from: (1) A temporary hepatic impairment of function, probably from a lowered hepatic circulation produced by injury, burning, subsequent operations, and anæsthesia, singly or often in combination; and (2) An acute loading of the blood-stream with bilirubin largely derived from the extravascular destruction of the non-viable population of red cells in stored blood. The transfusion acted like a bilirubin-loading test of liver function.

REFERENCES

ABELL, R. G., and PAGE, I. H. (1943), *Surg. Gynec. Obstet.*, **77**, 348.
BOYCE, F. F., and MCFETRIDGE, E. M. (1938), *Arch. Surg., Chicago*, **37**, 443.
DOBSON, E. L., and WARNER, G. F. (1954), *Fed. Proc.*, **13**, 36.
ENGEL, F. L. (1945), *J. Mt Sinai Hosp.*, **12**, 152.
GRABER, I. G. (1957), personal communication.
LAUSON, H. D., BRADLEY, S. E., and COURNAND, A. (1944), *J. clin. Invest.*, **23**, 381.
MOLLISON, P. L. (1951), *Blood Transfusion in Clinical Medicine*, p. 11. Oxford: Blackwell.
RICHARDS, D. W. (1943–4), *Harvey Lectures*, p. 217.
SCOTT, R., OLNEY, J. M., and HOWARD, J. M. (1955), "Systemic Response to Injury", *Battle Casualties in Korea*, Vol. 1, p. 149. Washington: U.S. Army Medical Service.
SEVITT, S. (1953), *J. clin. Path.*, **6**, 324.
— — (1957), *Burns; Pathology and Therapeutic Applications*. London: Butterworth.
SHACKMAN, R., GRABER, I. G., and MELROSE, D. G. (1952), *Brit. J. Surg.*, **40**, 193.
— — — — — — (1953), *Clin. Sci.*, **12**, 307.
TAGNON, H. J., ROBBINS, G. F., and NICHOLS, M. P. (1948), *New Engl. J. Med.*, **238**, 556.
ZAMCHEK, N., CHALMERS, T. C., and DAVIDSON, C. S. (1949), *Amer. J. Med.*, **7**, 409.

EXPERIMENTAL SURGERY

A PRELIMINARY REPORT ON A STUDY OF EXPERIMENTALLY PRODUCED TRICUSPID AND MITRAL VALVE REGURGITATION*

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THE pathological anatomy of many cases of serious mitral valve regurgitation is such that there is "virtually fibrous ankylosis of the valve mechanism" (Brock, 1952). It seems unlikely that the disordered anatomy of such a valve could ever be restored by any means known at present, and so far no mechanical contrivance devised has been really successful. This study is an attempt to apply a new conception to the problem. It is suggested that the disordered hæmodynamics associated with valvar regurgitation can be altered favourably by indirect methods.

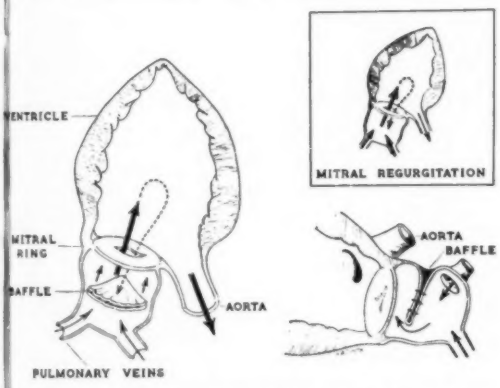


FIG. 85.—Mitral regurgitation with corrective intra-atrial diaphragm or baffle—edge free.

When mitral or tricuspid valve regurgitation results from any cause, part of the stroke volume at each ventricular systole is driven backwards into the atrium and its entering veins. During diastole the hæmodynamic state in the atria and afferent veins may be normal. In the case of mitral valve regurgitation, effective cardiac output into the aorta is reduced, and backward flow of blood causes enlargement of the left atrium and pulmonary congestion. Tricuspid valve regurgitation is associated with well recognized clinical signs, and measurements of back-flow in this condition, using dye dilution curves, have shown that more than half the total cardiac output in certain cases may be driven back through the leaking valve (Korner and Shillingford, 1955, 1957).

If the occasion arises to explore the left atrium of a patient suffering with mitral regurgitation, a backward stream of blood at high velocity can be felt during the short period of ventricular contraction. A partial obstruction placed in the path of this high velocity jet should reduce this backward flow of blood, and not only will pulmonary congestion be lessened, but forward cardiac output should be increased. Such a partial obstruction must not impede the stream of blood which flows at low velocity through the atrium into the ventricle during diastole.

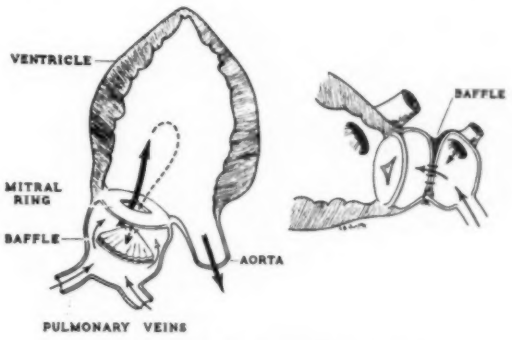


FIG. 86.—Intra-atrial diaphragm—edge fixed.

When a patient with serious mitral incompetence is examined under the X-ray screen it is often possible to demonstrate pulsation of the left atrium that is synchronous with ventricular contraction. It is obvious that a great deal of kinetic energy is being expended uselessly in this way. If the left atrium of such a patient were reduced in size and made almost inexpansible, and at the same time back-flow into the pulmonary veins reduced, this kinetic energy would be conserved, and forward cardiac output promoted.

Although a great deal has yet to be learnt of the hæmodynamics of the pulmonary veins, blood flows into the atrium at a comparatively low velocity. When the mitral valve leaks the back-flow of blood into the veins during ventricular systole is of high velocity and short duration. If the direction, the shape, or the size of the lumen of these veins is altered, this sudden high velocity back-flow should be reduced. Distortion of the afferent veins must not be so great as to interfere with the comparatively slow flow of blood into the atrium during diastole.

Finally, relief from the effects of pulmonary hypertension caused by mitral stenosis was given to a small group of patients for some years by the

* This work is proceeding with the help of a grant-in-aid from the Life Insurance and Medical Research Fund of Australia and New Zealand.

anastomosis of a pulmonary vein to an azygos vein (Sweet and Bland, 1949; Sweet, 1957). Should obstruction to pulmonary blood-flow result from any of the corrective manipulations described, this situation might be met by such an anastomosis.

On the basis of these theoretical postulates the various manœuvres to be described were tried in the experimental surgical laboratory using sheep. The two principal methods used have been (1) the creation of a diaphragm or 'baffle' across the atrium close to the point of regurgitation at the valve; and (2) alteration of the direction, or shape, or size of the lumen of the afferent veins.

METHODS

The Creation of a Baffle.—A selected portion of the wall of the atrium may be invaginated by placing a purse-string type of suture. If this suture is tightened, but left untied, a second layer can be placed. When this second layer has been completed, the first layer can then be withdrawn. In this way increasing areas of atrial wall can be inverted to create a diaphragm across the interior of the atrium. The final shape and direction of such a diaphragm is determined by the placement of these sutures and its rigidity by the number of sutures used.

Fig. 85 depicts such a diaphragm in which the edge has been left free. During ventricular diastole blood flows freely around and beneath this diaphragm to pass through the valve orifice into the ventricle. In ventricular systole a jet of blood is driven back momentarily against this semi-rigid diaphragm which acts as a baffle to oppose the sudden squirt of blood through the leaking valve orifice.

In *Fig.* 86 a diaphragm is shown which has been fixed at one site to the opposite or posterior wall of the atrium. This can be achieved by first approximating the front and back walls of the atrium, using either the finger or an instrument. One or more stitches are then passed through the apposed portions of atrial wall and tied, and concentrically arranged purse-string sutures placed as before.

In *Fig.* 87 this baffle is represented as being attached to the posterior valve cusp. This manœuvre requires a little practice and the attaching suture has to be guided into place by a finger in the atrium.

Reducing Back-flow in the Afferent Veins.—In *Fig.* 88 the angle of entry of the veins into the atrium is shown as being altered. In the experimental animal this can be achieved by mobilizing the vein and then attaching its wall to the adjacent part of the atrium with interrupted sutures. The theoretical effect of this is to allow unimpeded forward flow during diastole, but to reduce the back-flow which occurs at each ventricular systole.

Fig. 89 illustrates the manner in which a baffle may be fashioned to lie over the openings of the afferent veins.

Fig. 90 depicts the effect of narrowing the opening of the afferent vein and at the same time suturing the adjacent and venous walls so that this opening is advanced and elevated into the atrial chamber.

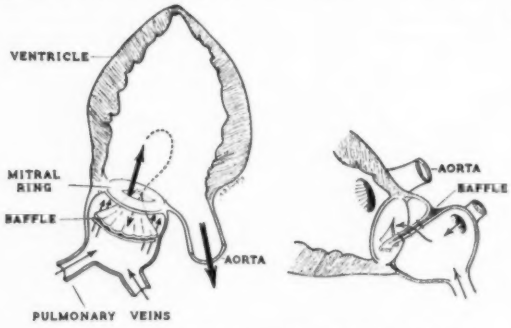


FIG. 87.—Intra-atrial diaphragm—edge attached to posterior valve cusp.

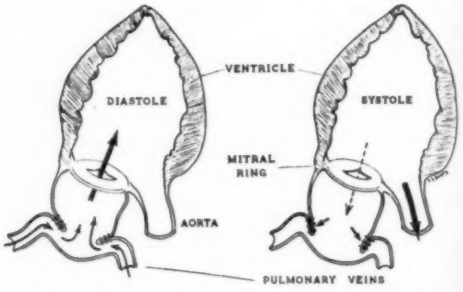


FIG. 88.—Alteration of angle of entry of pulmonary veins.

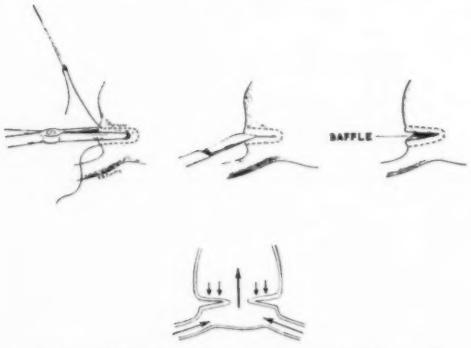


FIG. 89.—Baffle fashioned across entrance of veins opening into atrium.

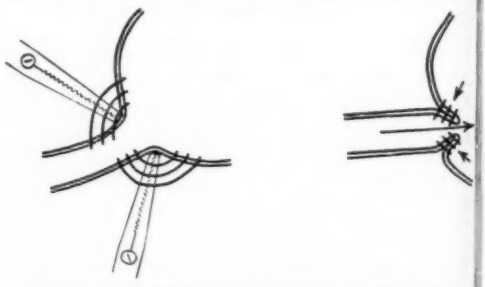


FIG. 90.—Orifice of afferent vein narrowed and elevated into interior of atrium.

A series of small baffles or 'vanes' can be fashioned as shown in *Fig.* 91. If these are placed with the 'vanes' directed towards the atrium, then the sudden backward squirt of blood which occurs at each ventricular contraction should be impeded. If the lumen of the vein is not narrowed too much the

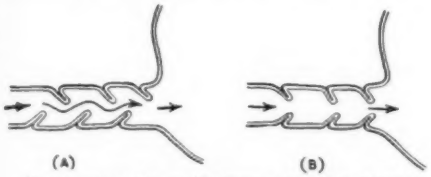


FIG. 91.—A, B, 'Vanes' fashioned to impede back-flow.

slow forward flow of blood which occurs during diastole should be unimpeded.

Fig. 92 illustrates how mattress sutures may be placed to convert the lumen of a vein from a single to a double channel. If two or more such sutures are placed in different axes, then the internal lumen of the vein will assume a tortuous or corkscrew shape. This will impede the flow of liquids at high velocity, but not those at low velocity.

EXPERIMENTAL PROCEDURES

General Remarks.—The animals used for these experiments were 'two-toothed ewes', weighing from 25 to 30 kg. Anæsthesia was induced and maintained by the intravenous injection of veterinary nembutal 25 mg. per kg. of body-weight. Ventilation with 100 per cent oxygen was maintained with an automatic respirator after the insertion of a cuffed intratracheal tube. A soda-lime canister was placed in the circuit to absorb carbon dioxide.

The Experimental Production of Tricuspid Regurgitation.—Tricuspid regurgitation is easy to produce in sheep, is well tolerated, and physiological observations can be made more readily on the right side of the heart than on the left side.

A trans-sternal incision at the level of the fifth intercostal space was used initially but was abandoned because of the frequency with which infection occurred. A right thoracotomy through the bed of the fifth rib is now used to approach the atrium. Tricuspid regurgitation is produced by inserting the finger through the right atrium to the right ventricle and avulsing one or even two chordæ tendineæ or a musculus pectinatus. A strong regurgitant jet can be felt and the atrium is seen to dilate at each ventricular systole.

In the weeks following this procedure most of the animals appear untroubled. A few develop ascites, venous pulsation in the neck veins may be apparent, and some appear to be ailing in that they obviously lack vigour.

Correction of Experimentally produced Tricuspid Regurgitation.—The right chest was re-opened some weeks after the original operation. The right atrium usually was so fixed by the adherence of the overlying pericardium that little, if any, dilatation was apparent even though both venæ cavæ might be greatly enlarged. In some animals quite appreciable enlargement of the right ventricle had occurred.

In order to place the baffle correctly the wall of the atrium was invaginated with the finger so that the regurgitant jet of blood could be felt. This site on the atrium was then marked and a series of purse-string sutures of monofilament nylon swaged on atraumatic needles were placed on ever widening

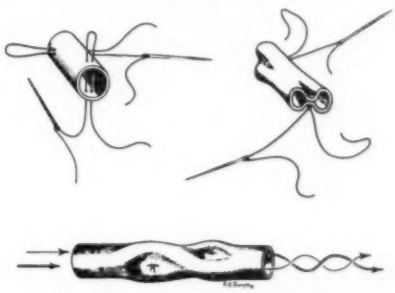


FIG. 92.—Alteration of lumen of vein.

circles outwards from this point. Inverting this portion of the atrial wall and tying the sutures resulted in the creation of a baffle in the interior of the atrium. The sutures were so placed that the

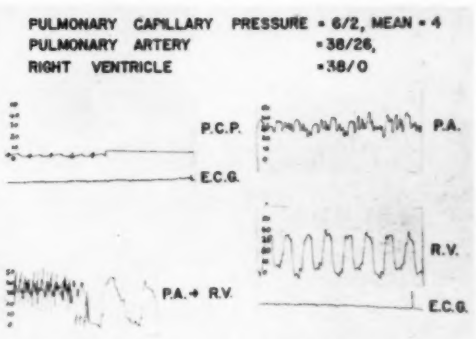


FIG. 93.—Catheterization: pressure recordings in a normal sheep.

resultant baffle came to lie just above the leaking valve.

Back-flow was further reduced by changing the angle of entry of the vena cava into the atrium (*see Fig.* 88) or by converting the single lumen of each vena cava into a double one (*see Fig.* 92).

The observations to be discussed later suggested that these manœuvres were successful in reducing back-flow so that efforts were then applied to the mitral valve.

The Experimental Production of Mitral Regurgitation.—If a chorda tendinea or musculus pectinatus is avulsed with the finger in order to produce mitral regurgitation in sheep, nearly all of the animals succumb to acute pulmonary œdema within twenty-four hours.

After various trials, the first consistently successful method found was to introduce a nerve hook through the atrial wall so as to engage either the posterior valve cusp or a tendon. If traction resulted

in marked systolic dilatation of the atrium the hook was judged to be correctly placed. A sudden tug then caused either rupture of the tendon or a tear of the cusp. These manipulations were repeated if it was felt that the degree of regurgitation was

PHYSIOLOGICAL OBSERVATIONS

Normal.—The pressure recordings in a normal sheep are shown in *Fig.* 93, where it can be seen that the pulmonary capillary venous pressure has a systolic reading of 6 mm. of mercury, and a diastolic

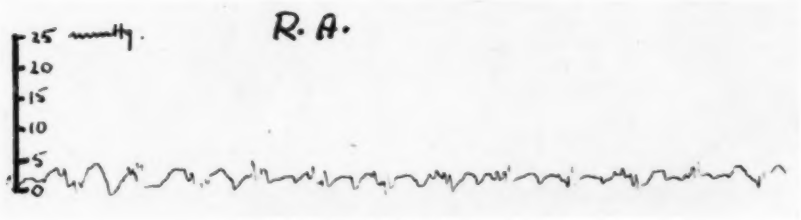


FIG. 94.—Normal right atrial pressure record.

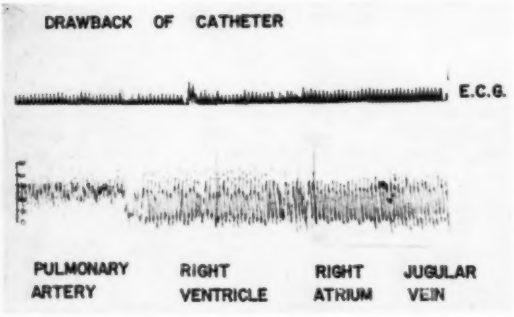


FIG. 95.—Withdrawal pressure record in an animal with tricuspid regurgitation.

reading of 2, with a mean of 4 mm. of mercury. The pulmonary artery pressure is $\frac{28}{2}$ and the right ventricular pressure $\frac{28}{0}$ mm. of mercury. *Fig.* 94 shows the pressure in the right atrium of a normal sheep. Although some of these readings are higher than usual the pressures and the form of the waves found on cardiac catheterization of the right side of a normal sheep are similar to the findings in humans.

Tricuspid Regurgitation.—*Fig.* 95 shows a continuous pressure recording in an animal with tricuspid regurgitation on withdrawing the catheter from the pulmonary artery up into the jugular vein. The position of the catheter was watched under the X-ray screen. In this pressure recording it can be seen that the form of the pulse wave continues ventricular in type right up into the jugular vein.

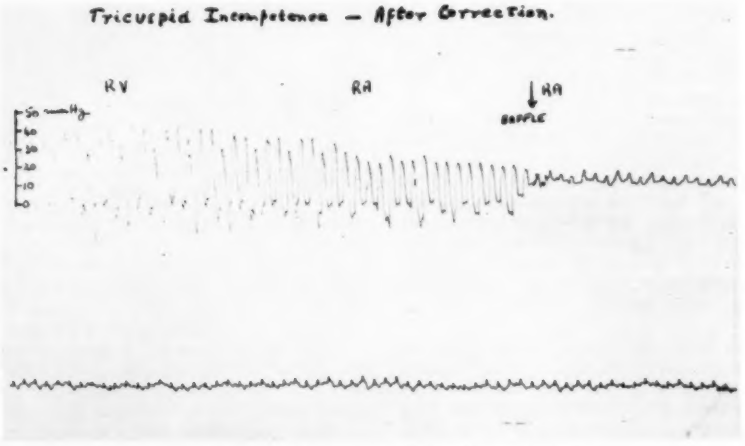
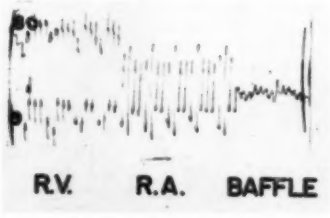


FIG. 96.—Surgical correction of tricuspid regurgitation.

insufficient. In order to leave the pericardial sac undisturbed, mitral regurgitation can be produced in the same way by entering the hook through the left superior pulmonary vein. Post-operatively these animals were given digoxin 0·5 mg., and 2 ml. of 'mersalyl' daily for a week, with, it was felt, definite benefit.

Corrected Tricuspid Regurgitation.—Corrective operations were performed on a number of sheep in which tricuspid regurgitation had been produced. *Fig.* 96 shows the findings on such an experimental animal. This pressure record shows that there is a slight gradient between the right ventricle and the right atrium where the tricuspid

valve had previously been avulsed. On withdrawing the catheter through the area of surgical correction it can be seen that there is a sudden abrupt change. There is a slight fall in pressure gradient, a rise in diastolic pressure and a very marked change in the pressure tracing in a normal animal as compared with one in which mitral regurgitation has been produced. The normal animal shows a mean pressure of a few millimetres of mercury. Animals in which mitral regurgitation has been produced show a pulmonary capillary venous pressure up to 30 mm. of mercury. The pressure in the pulmonary artery is usually not greatly raised and when pressures of 50 or more mm. of mercury were recorded obvious signs of stress were noted, and acute pulmonary œdema ensued in a number of animals.



Pressure in R.V. = 48/0
Pressure in R.A. = 30/2
Pressure above Baffle = 14/10

FIG. 97.—Surgically corrected tricuspid regurgitation.—withdrawal pressures.

In sheep No. 76 mitral regurgitation was produced, and right sided catheterization some weeks later showed pulmonary congestion with a mean pulmonary capillary venous pressure of 26. A cardiac catheter was entered into the carotid artery and passed into the left ventricle, the left atrium, and then into a pulmonary vein. In *Fig.* 99 the pressures recorded in this animal are shown. The pulmonary venous pressure is about 28 mm. of mercury. The pressure tracing in the left atrium is

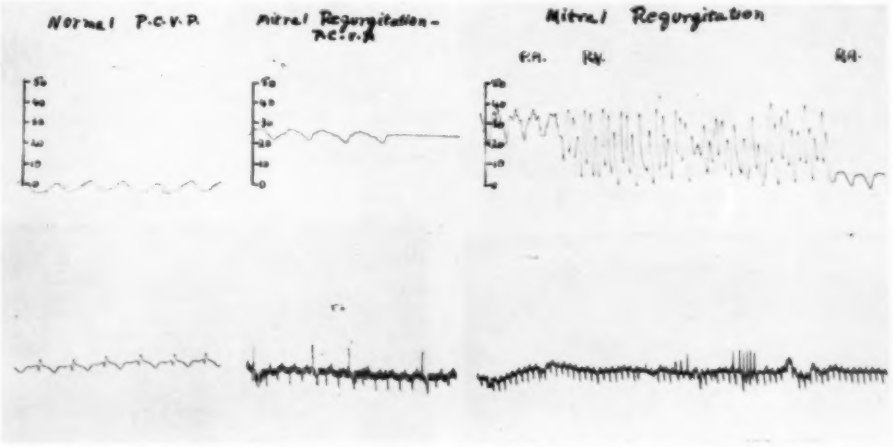


FIG. 98.—Pulmonary capillary venous pressure records in a normal animal compared to one with mitral regurgitation.

ventricular pressure wave. In this particular animal it is probable that the corrective surgical manipulations were excessive and slight venous obstruction may have been produced.

Fig. 97 shows the pressure records on experimental animal No. 86. Tricuspid regurgitation had been produced by avulsing with the finger a good deal of the tricuspid valve. A corrective baffle was fashioned immediately, and two weeks later this pressure recording was taken. It can be seen on withdrawing the catheter that there is a drop in pressure between the right ventricle and the right atrium as the catheter is withdrawn through the leaking tricuspid valve. On further withdrawing the catheter there is a sudden marked drop in pressure as the catheter passes across the area of surgical correction into the superior vena cava. The passage of the catheter was observed under the X-ray screen and these findings were confirmed on four separate occasions.

Mitral Regurgitation.—*Fig.* 98 shows the contrast between a pulmonary capillary venous much the same, whilst the left ventricular pressure has an average systolic value of 64 mm. of mercury.

RADIOGRAPHIC OBSERVATIONS

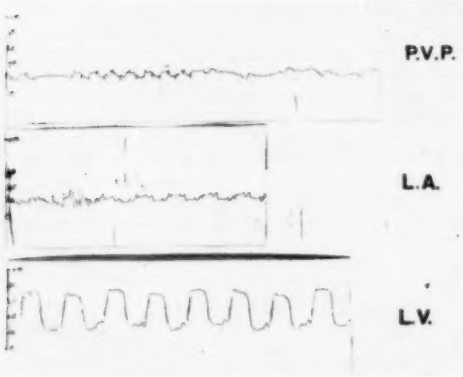
For all radiographic and screening procedures the animal was placed in the direct right lateral position making sure that the forelegs were well drawn towards the head to clear the thorax.

When the correct placement of the catheter was confirmed by fluoroscopy, the animal was then transferred to a horizontal Schonander film changer incorporating a fine line stationary Schonander grid. A Siemen's light beam diaphragm was found to give adequate protection to the injector from the beam. The injection of 8–15 mm. of 60 per cent urografin was made as rapidly as possible with manual pressure only. This took approximately 2–4 seconds. The first film was timed to occur about half-way through the injection and films were taken at the rate of two per second for 6–10 seconds.

Normal.—In *Fig.* 100 a complete angiocardiogram of a normal sheep used in this series is

shown. One exposure is taken before the left side of the heart has filled. The right auricular appendix, the right ventricle, the beginning of the pulmonary artery, the pulmonary veins, the left atrium, the left ventricle, and the aorta with its brachiocephalic trunk all can be seen.

Tricuspid Regurgitation.—In order to demonstrate the amount of leakage which may occur in tricuspid regurgitation, contrast medium was injected into the right ventricle of such an animal, and in *Fig.* 101 the amount of reflux of the medium can be seen. The findings in an animal on which tricuspid regurgitation had been produced, followed by a corrective operation, are shown in *Fig.* 102. Slight reflux of contrast medium back from the right ventricle can be seen, thus demonstrating visually that the back-flow of blood occurring in tricuspid regurgitation has been at least markedly reduced.



Pulmonary Venous Pressure = 28/16 mean = 20
Left Atrium = 26/16 mean = 20
Left Ventricle = 68/20

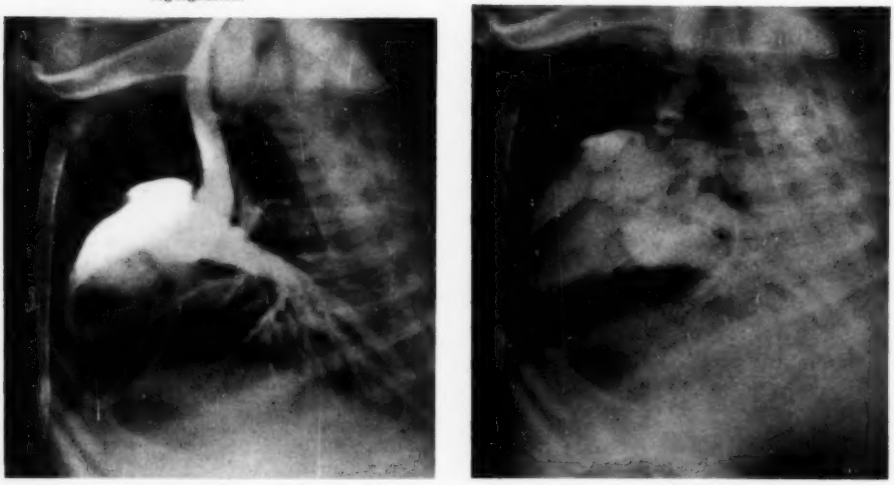
FIG. 99.—Left heart catheterization in animal with mitral regurgitation.

Mitral Regurgitation.—*Fig.* 103 is a radiograph taken after radio-opaque material has been injected into the left atrium of a normal sheep. The relative size of the atrium and ventricle should be noted and also the superior pulmonary vein which is visualized.

In another animal mitral regurgitation was produced and a mitral systolic murmur noted in the weeks following operation. Cardiac catheterization, however, failed to show any pulmonary hypertension. Contrast medium was then injected into the left ventricle and in *Fig.* 104 it can be seen that a very slight amount of reflux of the medium has occurred into the left atrium.

In experimental animal No. 76, mitral regurgitation was produced and the presence of pulmonary congestion verified by right heart catheterization. The left side of the heart was then catheterized (*see Fig.* 99) and contrast medium injected into the left ventricle. In *Fig.* 105 it can be seen that well-marked reflux of medium has occurred, that the left atrium is dilated in ventricular systole, and that medium has been driven back into the pulmonary veins which also are dilated.

In experimental animal No. 80, mitral regurgitation was produced, and eight weeks later a corrective baffle was fashioned by inverting the atrial wall as described and illustrated in *Fig.* 86. Two weeks later contrast medium was injected into the left ventricle, and in *Fig.* 106 it can be seen that there is reduction in back-flow of the medium and a filling defect caused by the baffle lying across the atrium.



A B

FIG. 100.—Angiocardiogram of normal animal showing contrast medium in A, the right side, and B, both sides of the heart.

DISCUSSION

The small size of the animals used in this study made it difficult to carry out some of the operative manipulations shown diagrammatically, even though similar procedures probably would be easy to effect in

human cases of mitral or tricuspid valve regurgitation. For example, in order to create an intra-atrial baffle in these animals, it was necessary to open the appendage and adjacent part of the atrium and divide numerous intersecting muscle bundles

FIG. 101.—Tricuspid regurgitation showing reflux of medium from right ventricle into right atrium.

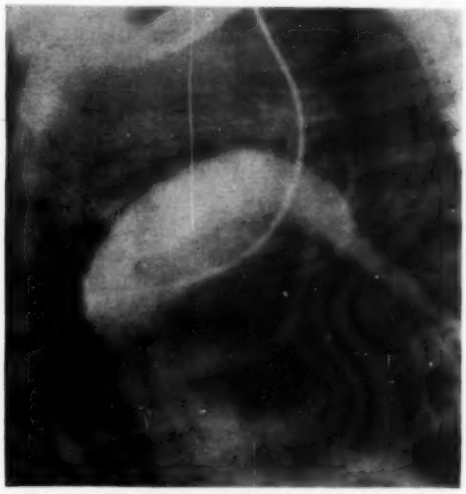


FIG. 102.—Tricuspid regurgitation after surgical correction.

FIG. 103.—Normal left atrium and superior pulmonary vein.

FIG. 104.—Slight mitral regurgitation.

before infolding of the atrial wall could be achieved.

Each one of these experiments has been concluded within a few weeks and so far it has not been possible to await the development of advanced degrees of atrial dilatation, nor to observe the effects of long-standing pulmonary or systemic venous congestion. Indeed, the virtue of doing so is in doubt in our minds as it is unlikely that the problems presented by human cases of mitral and tricuspid regurgitation can be reproduced in the experimental animal.

The objection has been raised that atrial dilatation will continue to increase after any of the described corrective procedures have been carried out. Although this will require further investigation, it has been noted during these experiments that when mitral or tricuspid valve regurgitation has been created through the atrium, the surgical trauma has invariably caused dense adherence of the pericardium to the heart. When the chest has been re-opened some weeks, or a month, later, no

enlargement of the atrium has been noted even when the afferent veins were obviously dilated.

With regard to the described methods of altering the blood-flow in the afferent veins, all of these manipulations have been carried out on the venæ cavæ. It will not be possible to effect some of these manœuvres on the pulmonary veins of sheep because of the small size of the vessels, but the venæ cavæ approximate in size to adult pulmonary veins and should be suitable to assess the effectiveness of each method. We propose also to conduct hydrostatic experiments using cadaver material.

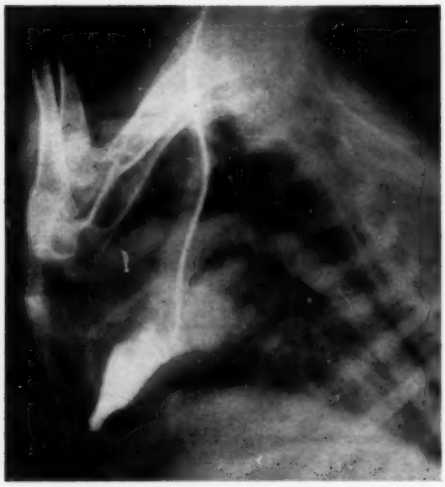


FIG. 105.—Mitral regurgitation sufficient to cause pulmonary congestion.

FIG. 106.—Mitral regurgitation after atrial baffle placed.

Tricuspid regurgitation due to dilatation of the valve ring is seen in the late stages of many forms of heart disease. It is possible that the methods here described might be applied as palliative treatment for certain types of heart failure, and the occasional success of inferior vena caval ligation would support such a suggestion.

SUMMARY

1. A new conception to meet the physiological disturbances of mitral and tricuspid valve regurgitation is suggested and various methods described.

2. Methods of producing valvar regurgitation in sheep are described and physiological and radiological observations on these animals are given.

3. Pressure recordings and angiocardiograms are submitted as evidence that a zone of resistance can be created to lessen the high velocity systolic back-flow of mitral and tricuspid valve regurgitation.

Acknowledgements.—It is impossible to acknowledge everyone who has contributed in some way to this work, but we would like to name Dr. W. Wilson Ingram, Director of the Institute of Medical Research, and Mr. F. F. Rundle, Head of the Unit of Clinical Investigation. Dr. Douglas Stuckey and Dr. R. G. Epps have advised us during the course of this study; Miss S. Bowman has prepared many of the records; and Miss S. Johnson has undertaken the typing. Finally, we would thank Sir Russell Brock for his interest in this work.

REFERENCES

BROCK, R. C. (1952), *Brit. Heart J.*, **14**, 489.
KORNER, P. I., and SHILLINGFORD, J. P. (1955), *Clin. Sci.*, **14**, 553.
— — — — (1957), *Brit. Heart J.*, **19**, 1.
SWEET, R. H. (1957), personal communication.
— — and BLAND, E. F. (1949), *Ann. Surg.*, **130**, 384.

SHORT NOTES OF RARE OR OBSCURE CASES

DUPLICATION OF SMALL INTESTINE

REPORT OF A CASE

By R. J. PUGH, D. B. FEATHER, and W. GOLDIE

FROM ST. JAMES'S HOSPITAL, LEEDS, AND THE DEPARTMENT OF PÆDIATRICS, UNIVERSITY OF LEEDS

It is well recognized that enterogenous cysts and duplications of the small intestine occur not infrequently in infancy and early childhood, and that a minority of these cysts and duplications are lined in part or in whole by gastric type mucosa (Gross, 1953). The following case seems worth putting on record, as not only was the duplication unusually extensive, but there was also a strikingly intimate association between the gastric mucosa which lined the duplication and the mucosa of the small intestine.

CASE REPORT

A 10-year-old boy was admitted to hospital on July 5, 1955, with a 3-month history of progressive pallor, weakness, and breathlessness. He had complained of intermittent abdominal pain and headaches over the same period, together with occasional bouts of vomiting, but he had attended school throughout. There was no loss of appetite or weight, and bowel actions had been regular. The boy's previous health had been good.

Clinical examination confirmed the pallor, but suggested no cause for it. A firm splenic enlargement to 2 finger-breadths below the left rib margin was noted, but physical examination was otherwise negative. A blood-count revealed a severe hypochromic anæmia (hæmoglobin 38 per cent (6·85 g. per cent), red cells 3·49 millions per c.mm., colour index 0·55), with no abnormality of white cells or platelets. Sternal marrow biopsy was carried out and this showed normoblastic hyperplasia with the appearances of severe iron deficiency; maturation of white cells was normal.

The patient remained well during the following two months; at the end of this period the anæmia had been corrected with iron by mouth and the spleen could no longer be felt. Tests for occult blood in the stools were, however, uniformly positive although radiological examination of the intestine and sigmoidoscopy failed to reveal any cause of gastro-intestinal bleeding. The possibility of hæmorrhage from an ulcer in a Meckel's diverticulum was considered, and when in October abdominal pain returned, together with frank melæna, surgical advice was sought and an exploratory operation decided on.

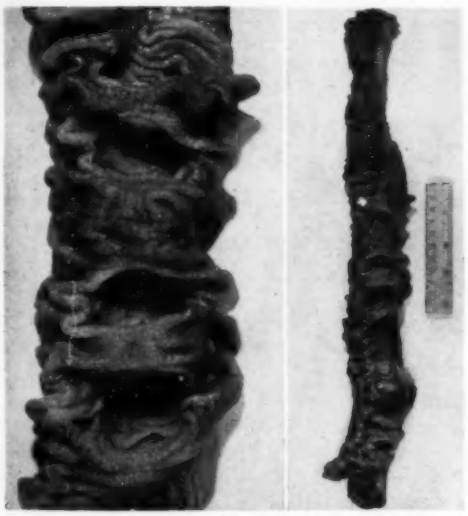


Fig. 107.—Larger piece of small intestine. In the upper third the gastric type epithelium is seen to the left of the specimen and the jejunal type to the right. In the lower two-thirds there is partial reduplication, and the lumen lined by gastric mucosa has been opened. The main passage lined by small-intestinal epithelium is seen through the gaps in the duplication. A higher magnification of this part is seen on the left.

Fig. 108.—Smaller piece of intestine. Two duplications, indicated by markers, are present. The first in the upper part of the specimen opens into the gut at either end. The second in the lower half did not communicate with the gut at either end.

Laparotomy was performed through a right paramedian incision. Preliminary examination of the abdominal viscera revealed no abnormality, but on more careful scrutiny a light inflammatory adhesion was found binding a short length of the lower jejunum to its own mesentery, and alongside this there was a shallow longitudinal groove. This was assumed to be evidence of

duplication of the intestine and preparations were made to resect the short length of jejunum involved. As a result of the peristalsis induced by the manipulations an extension of the longitudinal groove was seen to involve a much longer segment of jejunum. It was found necessary to resect over 2 feet of intestine, and continuity was restored by end-to-end anastomosis. Mesenteric glands were noted to be hyperæmic and the spleen reached the costal margin.

Convalescence was uneventful. When last seen over a year after the operation the boy was symptom-free and had a normal blood-picture.

PATHOLOGICAL REPORT.—The specimen consists of two pieces of small intestine 45 cm. and 20 cm. in length respectively. The intestine appears to be moderately dilated throughout, and there is an indefinite thickening both visible and palpable along the line of the mesenteric attachment. The serosa on either side of the mesentery is hyperæmic, especially at the lower end of the larger piece.

On opening the bowel it is seen that the mucosa at the upper end of the larger piece is of two distinct types (*Fig.* 107). Over approximately half its circumference is of small-intestinal type with close-set narrow folds running in a circular direction; the size and number of the folds suggest that it is jejunal rather than ileal. Along the mesenteric border there is a raised strip of mucosa characterized by broad close-set rugæ, the reddish velvety appearance of which forms a striking contrast to the pale yellow colour of the rest of the mucosa. The strip measures from 2 to 3 cm. in width, is about 0·5 cm. above the level of the adjacent mucosa, and runs along the intestine for a distance of 16 cm. This epithelium resembles closely gastric mucosa of fundal type.

Along the remainder of this larger piece there is partial reduplication of the intestine. The gastric-type mucosa becomes folded on itself to form a second lumen which lies along the mesenteric border and is approximately the same diameter as that formed by the small intestinal epithelium. The reduplication is incomplete and a

FIG. 109.—Section from larger piece of intestine. The junction between the epithelium of gastric fundal type above, and that of small-intestinal type below, is seen. The muscularis mucosæ is continuous. H. and E. (× 27.)

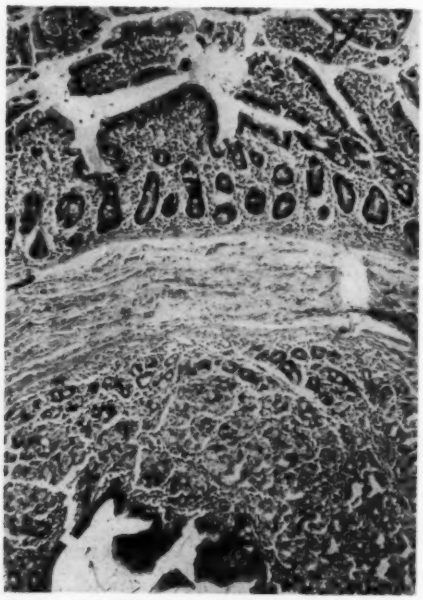


FIG. 110.—Section from open duplication in smaller piece of intestine. The small-intestinal epithelium lining the main channel is seen above and the gastric type epithelium lining the duplication below. There is a common circular muscle. H. and E. (× 90.)

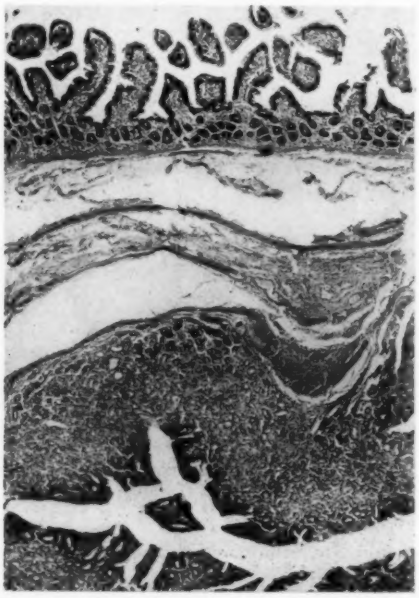


FIG. 111.—Section from imperforate duplication in smaller piece of intestine. The main lumen lined by small-intestinal type epithelium is seen above and the duplication lined by gastric epithelium below. H. and E. (× 27.)

number of large gaps are left which allow free communication between the two lumina.

The mucosa of the small piece of gut is of jejunal type, but extending along the greater part of its length, again in the line of the mesenteric border, is a second lumen (*Fig.* 108). It occurs in two parts and these are separated by a gap of about 4 cm. The upper part, which measures 8 cm. in length and 1·5 cm. in diameter, communicates at either end with the intestine proper by openings about 1 cm. in diameter. There are also at least four slit-like communications along its course, but these can only be seen when the folds of jejunal mucosa are drawn apart. The second part of the reduplication is 6 cm. in length and up to 1 cm. in diameter. The mucosa at either end is pouting, but apparently imperforate and the only communication found between this channel and the intestine proper is a small slit between the mucosal folds about half-way along. The reduplicated portions are again lined by gastric-like mucosa and they have well developed muscular layers.

Both pieces of intestine contain much changed blood, but no bleeding points are seen in either, nor are any areas of ulceration identified. While the gastric type of mucosa reaches practically to the edge of the upper end of the larger piece of intestine, about 4 cm. at the lower end of the smaller piece is normal, in that there is no reduplication.

Histology.—Many sections from both pieces of intestine have been studied. In the upper part of the larger piece of intestine the raised strip of mucosa is of gastric fundal type with prominent oxyntic cells (*Fig.* 109). The rest of the mucosa is small-intestinal in type and the transition between the two kinds is abrupt and almost linear. There is no break in the underlying muscularis mucosæ, submucosa, muscularis, and serosa, all these layers being common to both types of epithelium.

The gastric mucosa is lightly infiltrated by neutrophils and eosinophils and a few lymphoid follicles are seen in the submucosa.

All the reduplicated portions of intestine are lined by gastric mucosa of fundal type and they have their own muscularis mucosæ, submucosa, and muscular layers. The lumen away from the mesentery is lined by normal jejunal mucosa. Where the two lumina are contiguous the muscular layers are blended and inseparable (*Figs.* 110 and 111). In the bridges between the gaps where reduplication is incomplete the gastric mucosa on the side of the mesentery and the jejunal on the opposite side have a common muscularis, and there is an abrupt transition between the two different types of mucosa at the edges of the bridges. In none of the sections examined has there been any intermingling of gastric and intestinal glands.

In some areas there are great aggregations of lymphoid follicles in the jejunal submucosa with atrophy of the overlying villi. Scanty eosinophils are present in the gastric mucosa almost everywhere; they are rather more numerous in the reduplication in the smaller piece of intestine. No ulceration of the jejunal mucosa is seen.

DISCUSSION

Duplications may be found at any level in the digestive tract, but are most frequent in the ileum, especially adjacent to the ileocæcal junction; of the 68 examples described by Gross (1953) 25 were in the ileum. In their simplest form they exist as cysts of varying size, but more elaborate tubular duplications are not infrequent and these may reproduce in detail the parent bowel, even to the inclusion of a reduplicated appendix (Menten and Denny, 1945), and acute inflammation of such an extra appendix has been described (Saleeby, Zollinger, and Ellison, 1954). Triplication of the bowel has also been described (Gray, 1940) while Ladd and Chisholm (1943) reported the occurrence of rectal duplication associated with a double uterus and vagina. Bremer (1944) describes three types of duplication according to the length and degree of separation from the bowel.

According to Ladd and Gross (1940) and to Poncher and Miller (1933) most are short, and they are attached to the mesenteric surface of the adjacent bowel by a continuation of the circular muscle. They have their own mucosal, submucosal, and smooth muscle layers, and their mucous membrane may resemble that of the adjacent bowel or be representative of another part of the digestive tract, usually the stomach; in one case described by Nolan and Lee (1953) a spherical duplication communicating with the œsophagus was lined by columnar ciliated epithelium. Frequently the lumen of the duplication does not communicate with the adjacent bowel, but in a minority communication is affected by one or two ostia, while rarely, as in the present example, more intimate communication is present (Gross, 1953).

The majority of reported examples have presented early in childhood. Only 6 patients in the series reported by Gross were over 5 years of age, and Nolan and Lee could find only 19 examples of the condition in adults. Intestinal obstruction is the usual mode of presentation, and this may be preceded by colic, possibly due to progressive distension within the duplication. Pachman (1939) described ileocæcal intussusception caused by duplication in an infant of 8 months.

Bleeding from the bowel is another mode of presentation, and according to Gross this is most frequently seen in the long tubular duplications. The hæmorrhage may be due either to necrosis from local interference with the blood-supply, or it may be due to mucosal ulceration in the parent bowel caused by acid secretions from gastric mucosa lining the duplication. Examples of the latter occurrence have been described by Fisher (1950), Wooler (1950), Poncher and Miller (1933), and Thomson, Wilson, and Cunningham (1954). Black and Benjamin (1936) reported an infant who presented with hæmorrhage from the intestine and died suddenly as a result of perforation of an ulcer in the bowel. A malabsorption syndrome in an adult who made a complete recovery following removal of an ileal duplication was described by Slomovitz, Cash, and Enzer (1948).

The derivation of these duplications has aroused much speculation. Evans (1929) suggests that they are due to a failure of regression of the diverticula which Lewis and Thyng (1907) first observed in the developing entoderm of the 20–30-mm. human embryo. These diverticula arise as minute buds from the gut epithelium into the subepithelial connective tissue. While agreeing that such a mechanism may explain the development of a thin-walled cyst devoid of muscle layers, Bremer (1944) attributes an earlier origin to enterogenous duplication. He cites the observations of Johnson (1910) who described how the intestinal lumen in the 10-mm. embryo became partially obliterated by the disproportionate rapidity of epithelial growth. Secretion which normally occurred within the plugs of epithelium filling parts of the bowel formed

vacuoles which were usually arranged in chains or rows lengthwise along the lumen. Normally, as the gut lengthened, these vacuoles opened into the lumen and disappeared, but exceptionally, the coalescence of these vacuoles might form longitudinal channels which could communicate with the main lumen or be independent. Bremer believes that duplications are the result of persistence of these subsidiary channels, which would become lined by columnar epithelium and bounded by basement membrane dividing them from the main bowel; submucosal layers would appear concurrently with normal intestinal development.

This view adequately explains the occurrence of a common circular muscle, the variability of any communication with the parent bowel, and the elaborate mirroring of the gut which may occur. The fact that these duplications may be lined by gastric mucosa in no way excludes this theory. At the stage when these vacuoles are formed, the small intestine measures from 2 to 2·5 mm. and disproportionate overgrowth of primitive gastric epithelium along a part of the small intestine might well occur.

We wish to thank Professor W. S. Craig for allowing us access to his clinical notes. For the photography we are indebted to Mr. J. Hainsworth, Department of Medical Photography, St. James's Hospital, Leeds.

REFERENCES

BLACK, R. A., and BENJAMIN, E. L. (1936), *Amer. J. Dis. Child.*, **51**, 1126.
BREMER, J. L. (1944), *Arch. Path.* (*Lab. Med.*), **38**, 132.
EVANS, A. (1929), *Brit. J. Surg.*, **17**, 34.
FISHER, H. C. (1950), *Arch. Surg., Chicago*, **61**, 957.
GRAY, A. W. (1940), *Arch. Path.* (*Lab. Med.*), **30**, 1215.
GROSS, R. E. (1953), *The Surgery of Infancy and Childhood: Its Principles and Techniques*, 221. Philadelphia: W. B. Saunders.
JOHNSON, F. P. (1910), *Amer. J. Anat.*, **10**, 521.
LADD, W. E., and CHISHOLM, T. C. (1943), *Amer. J. Dis. Child.*, **66**, 629.
— — and GROSS, R. E. (1940), *Surg. Gynec. Obstet.*, **70**, 295.
LEWIS, F. T., and THYNG, F. W. (1907), *Amer. J. Anat.*, **7**, 505.
MENTON, M. L., and DENNY, H. E. (1945), *Arch. Path.* (*Lab. Med.*), **40**, 345.
NOLAN, J. J., and LEE, J. G. (1953), *Ann. Surg.*, **137**, 342.
PACHMAN, D. J. (1939), *Amer. J. Dis. Child.*, **58**, 485.
PONCHER, H. G., and MILLER, G. (1933), *Ibid.*, **45**, 106.
SALEEBY, R. G., ZOLLINGER, R. M., and ELLISON, E. H. (1954), *Surgery*, **36**, 306.
SLOMOVITZ, Z., CASH, I. I., and ENZER, N. (1948), *Gastroenterology*, **11**, 528.
THOMSON, T. J., WILSON, J. H., and CUNNINGHAM, G. L. W. (1954), *Ibid.*, **26**, 774.
WOOLER, G. H. (1950), *Brit. J. Surg.*, **37**, 356.

EMERGENCY GASTRECTOMY FOR BLEEDING DUODENAL ULCER IN A PATIENT WITH SEVERELY IMPAIRED RESPIRATORY FUNCTION

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MAJOR surgery can be performed successfully on patients in whom respiratory function is greatly impaired. However, many problems may arise, and we record this case in the hope that the method of management will prove helpful to those confronted with similar difficulties.

CASE REPORT

A man, aged 67, was admitted to St. Mary Abbot's Hospital on Feb. 20, 1957, following a severe melæna. A similar but lesser hæmorrhage had occurred in January, 1956. He complained of having had epigastric pain and indigestion for the past year.

He also gave a history of chronic bronchitis and increasing breathlessness for five years, with exacerbations each winter. In March, 1955, he was admitted to hospital suffering from a left lower lobe pneumonia; later, as an out-patient, he received treatment for bronchiectasis.

ON EXAMINATION.—He was extremely ill and very pale, and his breathing was rapid and laboured; the thoracic cage moved poorly. The pulse was regular and the rate 106 per minute; the blood-pressure was 120/60 mm. of mercury. Palpation of the abdomen revealed no abnormality other than epigastric tenderness. After rectal examination, dark blood could be seen on the tip of the gloved finger.

Hæmoglobin was 3·9 g. per cent. Radiography of the chest showed marked fibrosis in the upper zones and basal bronchitis and emphysema.

During the next thirty-six hours he had three further hæmorrhages in the form of melæna. The blood-pressure was maintained above 100 mm. of mercury, systolic, by repeated blood transfusions (9 pints).

A partial gastrectomy was done on the second day after admission to hospital.

AT OPERATION.—The blood-pressure was 110/65 mm. of mercury. The patient's throat and upper air-passages were full of sputum which he was too weak to expectorate, and there were moist crepitations at both lung bases, more marked on the left. He was slightly cyanosed.

Immediately prior to operation a bronchoscopy was performed under local anæsthesia (4 per cent xylocaine), and a large amount of sputum was sucked out, mainly from the left lower lobe bronchus. Following this he was much improved.

He was then given a general anæsthetic and the abdomen opened through a right upper paramedian incision. There was a large ulcer on the posterior wall of the first part of the duodenum, penetrating the pancreas. Closure of the duodenal stump was difficult, and at the

end of the operation, through a lateral stab wound, a drainage tube was inserted down to the stump in case of leakage. An antecolic anastomosis with a Hofmeister valve was made between the proximal jejunum and the gastric remnant. Two pints of blood were transfused during the operation, which lasted one hour and forty minutes.

The anæsthetic technique was as follows. Premedication was with atropine gr. $\frac{1}{100}$ intravenously. (No morphine, pethidine, or barbiturate had been given in the preceding twelve hours.) Anæsthesia was induced with cyclopropane and oxygen, followed by nitrous oxide, oxygen, and ether. The patient was intubated with a No. 10 cuffed endotracheal tube.

It was thought that fewer difficulties would be encountered if he was allowed to breathe spontaneously. However, he could not ventilate adequately and he became deeply cyanosed; 7 mg. of d-tubocurarine was injected intravenously and controlled respiration was begun, nitrous oxide and oxygen being used at the rate of 5 litres and 2 litres per minute respectively. The ether was turned off. The patient's colour immediately became pink and remained so for the rest of the operation. Additional doses of d-tubocurarine were given, a total of 24 mg. being used. A carbon dioxide absorber was included in the anæsthetic circuit.

At the end of the operation, spontaneous respiration did not return. Carbon dioxide was allowed to accumulate; this produced a flickering respiratory movement. Atropine gr. $\frac{1}{60}$, followed by prostigmine in two divided doses each of 1 mg., were given intravenously and fifteen minutes later 5 ml. of nikethamide was injected by the same route. These drugs produced no respiratory response.

During this time inflation of the lungs was continued with nitrous oxide and oxygen (5 litres : 2 litres) and with the carbon dioxide absorber in the circuit. The absorber was taken out of the circuit for a few minutes and carbon dioxide was added to the nitrous oxide and oxygen mixture. The stimulus of an increased concentration of carbon dioxide did not affect respiration. The patient's colour was pink, his blood-pressure and pulse were satisfactory, but he was apnœic and deeply unconscious.

Potassium deficiency was considered as a possible cause of the continued apnœa. The serum potassium was estimated and found to be within normal limits (4·7 mEq.). The alkali reserve was 31 mEq./l., suggesting the absence of carbon dioxide retention.

However, respiratory acidosis due to carbon dioxide retention could not be excluded, as estimations of alveolar and arterial carbon dioxide tensions were not made.

Both during and after the operation the patient was well oxygenated. It was argued that as a result of chronic respiratory disease, the stimulus of a mild degree of anoxia was necessary to make the respiratory centre resume activity, and that if he was inflated with a mixture of gases in which the oxygen concentration did not exceed 20 per cent, spontaneous respiration might return.

A Mark 2 Beaver respirator was obtained and connected to the endotracheal tube and the patient's lungs were inflated with air. Almost immediately, respiratory movements became apparent and reflex activity began to return.

During the following eight hours respiration slowly improved and coma lightened. The respirator was used almost continuously, short intervals being allowed for observation of the patient's respiratory efforts. Twelve hours after the end of the operation he regained consciousness. The endotracheal tube was removed. Within five minutes he became drowsy, his colour deteriorated, and twitching of the limb and facial musculature occurred. It was obvious that his own respiratory efforts were insufficient to prevent him becoming anoxic. The endotracheal tube was re-inserted and artificial respiration restarted. In a few minutes he became alert again.

In the course of the next twelve hours he was at no time able to remain off the respirator for more than ten minutes without becoming anoxic.

It seemed likely that he would be dependent on artificial respiration for several days at least; tracheotomy was therefore performed, following the injection of a small dose of pentothal (0·4 g.) and a very shortened cuffed endotracheal tube was inserted through the opening in the trachea and connected to the Beaver respirator.

Six hours after the partial gastrectomy, the blood-pressure fell from 120 to 70 mm. of mercury, systolic. The transfusion was speeded up and methedrine was injected, 15 mg. intravenously and 15 mg. intramuscularly. These measures were without effect. A noradrenaline drip, however, rapidly restored the pressure and maintained it for the following thirty-six hours, after which time it was discontinued.

During the first twenty-four hours after operation, the pulse and blood-pressure were charted every half-hour. The bronchi were kept clear by suction through the endotracheal tube at 15-minute intervals, and the patient's position was changed as frequently as possible to encourage drainage from the lungs and to avoid venous thrombosis.

When he regained consciousness, a physiotherapist postured him and percussed his chest every two hours. Initially, radiographs of the chest were taken twice a day.

The Ryle's tube was aspirated half-hourly and the intake and output of all fluid was carefully charted. One million units of penicillin and 1 g. of streptomycin were injected twice a day.

Electrolytes, blood-sugar, blood-urea, and hæmoglobin were estimated during the initial period of coma, and with the exception of the blood-sugar, were thereafter determined daily.

Six days after operation, the patient was able to breathe adequately without the respirator for one hour; when an attempt was made to extend this period to two hours, he became anoxic, accumulated carbon dioxide, and had a steep rise in blood-pressure. Thereupon the Beaver machine was reconnected. By the fourteenth post-operative day he was able to manage entirely without the respirator. From then on, the tracheotomy was allowed gradually to close and the Ryle's tube, through which he had been fed hourly for the previous ten days, was removed.

Several days after the partial gastrectomy, the anticipated discharge of bile from the duodenal stump began via the drainage-tube. Although copious at first, it gradually lessened and finally ceased two weeks later.

Many of the superficial veins of the limbs were thrombosed following the numerous transfusions. In addition, tenderness along the line of a posterior tibial vein aroused suspicion of deep vein thrombosis. Heparin therefore was injected 6-hourly for a period of three weeks, beginning on the fifth day after operation.

DISCUSSION

This patient was primarily an abdominal breather; his maximum chest expansion was $1\frac{1}{2}$ in. He depended almost entirely on his diaphragmatic movement, and when this was to a large extent put out of action by an upper abdominal operation he became a severe respiratory cripple. As convalescence progressed, he was gradually 'weaned off' the respirator, and after two weeks was able to ventilate sufficiently by his own efforts.

It did not seem likely that the use of any other anæsthetic technique would have avoided the necessity for prolonged artificial respiration during the period following operation.

The Beaver machine was found to be most reliable, easy to work, and simple to adjust.

The procedure adopted in this case proved to be a satisfactory solution to this particular problem.

The survival of this patient was in large part due to the untiring and constant efforts of both the nursing staff and the physiotherapists.

We would like to thank Dr. A. J. W. Beard, Consultant Anæsthetist and Lecturer in Anæsthesia to the Postgraduate Medical School, for his helpful advice and criticism.

A CASE OF BILATERAL HERNIÆ THROUGH PETIT'S TRIANGLE WITH TWO ASSOCIATED ABNORMALITIES

By R. J. W. ADAMSON, Maidstone

Lumbar hernia may be acquired or congenital, single or bilateral. Only 125 cases have been reported in the world literature, of which only 2 have been bilateral Petit's herniæ (Coley, 1921; Flinckinger and Masson, 1946).

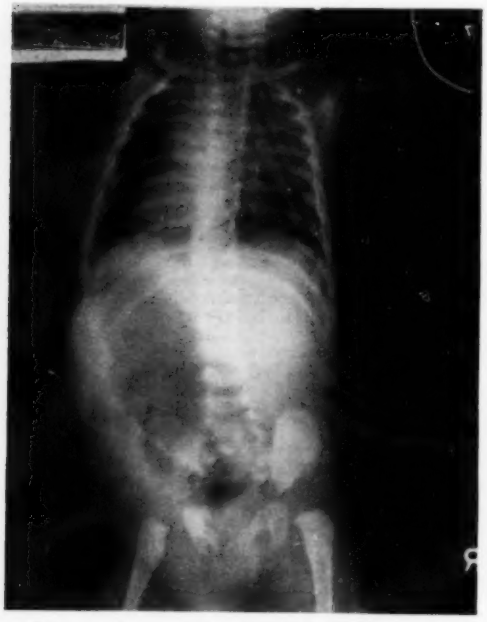

Fig. 112.—Anteroposterior view with enlarged thymus in left superior mediastinum.

The presumptive reason for the comparative rarity of the congenital types of Petit's hernia may be ascribed to its anatomy. The triangle of Petit depends for its presence on the origins of the external oblique and latissimus dorsi muscles from the iliac crest; if they meet, there is no triangle. If a triangle is present, its floor is formed by the internal oblique muscle. If there is a rise of intra-abdominal pressure, the overlying internal oblique muscle responds by contraction, and there is no weakness. If, however, the aponeurosis of the internal oblique muscle extends more laterally than is usual, then the intra-abdominal rise of pressure tends to push and stretch the fibrous aponeurosis before it, thus acting as a major factor in the production of this hernia.

Fig. 113.—Left lateral view.

CASE REPORT

A first-born male child was found at birth to have a hernia through the left Petit's triangle.

The child was admitted at 10 weeks of age to hospital, when it was noted that he had several attacks of vomiting for no apparent cause, and as his condition appeared satisfactory he was operated on when 11 weeks old. Straight and lateral radiographs of the abdomen were taken before operation (*Figs.* 112, 113).

At operation a transverse incision (6 cm.) was made over the hernia and a deficiency in Petit's triangle,

through which two fingers could be passed, was found. A hernial sac was present which, when opened, was found to contain pelvic colon, partially adherent to the sac. This sac was partly removed and the pelvic colon and adherent part of the sac returned to the peritoneal cavity. The peritoneum was closed with catgut. The defect was closed by a nylon darn to the extraperitoneal tissues and transversalis fascia. The latissimus dorsi and external oblique muscles were approximated with two catgut mattress sutures which included the fibres of the internal oblique muscle.

The post-operative recovery was normal until four days after operation when visible peristalsis in the epigastrium and projectile vomiting were noted for the first time at nearly 12 weeks of age.

On examination no palpable lump was found in the epigastrium to confirm a hypertrophic pyloric stenosis and the child responded completely to medical treatment. At the same time a right inguinal hernia and a right lumbar hernia were seen also for the first time.

The infant was discharged home on the sixteenth post-operative day, having the right lumbar hernia well controlled by adhesive strapping over a pad. When seen in out-patients two weeks later the hernial repair was satisfactory, the right lumbar hernia controlled, the right inguinal hernia not seen and no further vomiting had occurred.

SUMMARY

This case is presented because :—

1. Only 2 previous cases of bilateral herniæ through Petit's triangle have been found in the world literature.

2. A right inguinal hernia was seen.

3. Projectile vomiting with visible peristalsis occurred in a first-born male child of nearly 12 weeks of age, suggesting a diagnosis of pylorospasm, since no palpable lump was felt.

Acknowledgement is made to Mr. E. H. C. Harper, surgeon to the West Kent General Hospital, for permission to report this case, and for his help in its preparation, and to Professor R. J. Last of the Royal College of Surgeons for his help, and to Dr. J. M. Corall and X-ray staff of the West Kent General Hospital.

REFERENCES

COLEY, W. (1921), *Ann. Surg.*, **74**, 650.
FLINCKINGER, F. M., and MASSON, J. C. (1946), *Amer. J. Surg.*, **71**, 752.

REVIEWS AND NOTICES OF BOOKS

The Healing of Wounds. A Symposium of Recent Trends and Studies. Edited by MARTIN B. WILLIAMSON, Ph.D., Professor of Biochemistry, Stritch School of Medicine, Loyola University, Chicago. 8 × 5 in. Pp. 202 + xii, illustrated. 1957. New York: McGraw-Hill Publishing Company Ltd. 54s. 6d.

A SYMPOSIUM on the healing of wounds was held at the Stritch School of Medicine, Loyola University, Chicago, under the direction of Dr. Martin B. Williamson, and this volume is a record of the papers delivered. The subjects range over the biochemical and molecular aspects of wound healing and within the compass of 200 pages is contained a wealth of information which is of value to experimentalists, to surgeons, and to gynæcologists as well as to practising physicians.

The problem of the relation of the healing of wounds to the metabolism of proteins and amino-acids is dealt with by the editor and the importance of cystine and methionine in the healing process is stressed. The part played by sulphur is emphasized and the conversion of methionine sulphur to cystine sulphur and so to sulphate sulphur is traced.

Subsequent essays elaborate the role of these amino-acids and an important contribution by Fromm and Nordlie defines the part played by vitamin C in the formation of collagen upon which the strength of a healing wound so largely depends—an aspect which is dealt with in a separate essay by Marbach. Taubenhaus discusses the effects of hormones on the healing of wounds, particularly in relation to the formation of granulation tissue which cortisone is found to inhibit. On the other hand, desoxycorticosterone and aldosterone are found to stimulate granulations, as does the growth hormone of the anterior pituitary.

Whilst the early part of the book is of great theoretical interest, it is the last three chapters on "The Healing of Muscle", by David Jones, "Incisions used in Gynæcology", by Herbert E. Schmitz, and especially "Clinical Approaches to the Concepts of Wound Healing", by Harold B. Haley, which will appeal to the practising surgeon and gynæcologist.

Apart from stressing the importance of the fundamental details of operative technique which every surgeon is taught but which he may, with the passage of time, tend to neglect, there is a strong insistence by these authors on the superiority of transverse abdominal incisions over vertical ones. Dehiscence is considered in detail and the following factors are listed as being contributory: (1) Obesity, (2) Hot weather, (3) Malnutrition, (4) Hæmorrhage, and (5) Excessive suture material buried in the wound.

Whatever the reader may think of the individual recommendations which are made, this book clearly and interestingly outlines the present position of our knowledge on most of the theoretical and practical aspects of wound healing. It will promote thought and encourage discussion; it should be read by every practising surgeon.

Introduction to Dental Anatomy. By JAMES HENDERSON SCOTT, D.Sc., M.D., L.D.S., Reader in Anatomy for Dental Students, The Queen's University, Belfast, and NORMAN BARRINGTON BRAY SYMONS, M.Sc., B.D.S., Senior Lecturer in Dental Anatomy and Histology, and Curator of the Dental Museum, The University of St. Andrews at the Dental School, Dundee. 8¾ × 5½ in. Pp. 344 + xii, with 219 illustrations. 1958. Edinburgh and London: E. & S. Livingstone Ltd. 42s.

THE first edition of this book, published some six years ago, received excellent reviews because it fulfilled a very definite long-felt want for dental students. In this second edition the authors have produced a much better book; in fact, the greater part of the book has been re-written, and some fifty new photographs and diagrams have been added.

This book should make a great appeal not only to dental students but to all anatomists, for they will find a

wealth of material within its pages. This material would be difficult to obtain from other sources.

An outstanding reference book.

Endocrine Aspects of Breast Cancer. Proceedings of a Conference held at the University of Glasgow, 8th–10th July, 1957. Edited by ALASTAIR R. CURRIE, B.Sc., M.B., F.R.C.P. (Ed.), Senior Lecturer in Pathology, University of Glasgow; Consultant Pathologist, Royal Infirmary, Glasgow. With a Foreword by C. F. W. ILLINGWORTH, C.B.E., M.B., Ch.M., F.R.C.S. (Ed.), F.R.F.P.S., Regius Professor of Surgery, University of Glasgow. 8¾ × 5¼ in. Pp. 340+xvi, with 7 figures. 1958. Edinburgh: E. & S. Livingstone Ltd. 37s. 6d.

THIS volume contains the Proceedings of a Conference held at the University of Glasgow in July, 1957. The Conference, which was called together at the suggestion of Professor Illingworth, was a highly successful one and dealt with all the endocrine aspects of breast cancer.

There are some 51 papers with excellent synopses of the discussions and critical commentaries; those by Professor Marrian are particularly helpful yet critical.

The clinical results of oöphorectomy, adrenalectomy, hypophysectomy, radio-active implants into the pituitary are all recorded. The histochemical examinations of the pituitary and adrenal glands are discussed. The enzymic activity of the adrenal cortex and the hormonal content of the human pituitary glands are fully described.

Important assays of œstrogens, 17-oxosteroids, 17-oxogenic steroids, and pituitary hormones before and after surgical ablation are recorded. Sir Stanford Cade, who has probably operated upon more adrenals than any other surgeon in this country, gives his results of 170 patients with disseminated breast cancer who were submitted to adrenalectomy and gonadectomy. Cade is certain that no convincing evidence has yet been produced that hypophysectomy is in any way superior to adrenalectomy.

The book should prove of real value to all those surgeons, pathologists, and biochemists who are interested in breast cancer.

It will prove a very valuable reference volume.

Anesthesia. A Manual for Students and Physicians. By STUART C. CULLEN, M.D., Chairman, Division of Anesthesiology, Department of Surgery, State University of Iowa Hospitals. Fifth edition. 8 × 5¼ in. Pp. 295, with 37 illustrations. 1957. Chicago: The Year Book Publishers Inc. (London: Interscience Publishers Ltd.) 42s.

THE minor changes which have been made in this edition do nothing to increase its value. It is now represented as "a manual for all students (undergraduate and graduate) and physicians". There is much in it to bewilder the student, and not a little to exasperate the expert, such as the inclusion of a number of puerile cartoons, the omission of any reference to retrolental fibroplasia in discussing the harmful effects of oxygen therapy, and the statement that hypothermia permits complete interruption of the circulation for thirty minutes.

Though quite a lot of information is conveyed, the book suffers from the inability of its author to write concise English. For instance, he will write "It is important to the patient's welfare that this restlessness be examined thoroughly with respect to the reason for its development" when he means that it is important to find out why the patient is restless.

As an example of the lack of balance that may well lead the student astray, the important subject of cardiac arrest is tacked on to the chapter on ventilation as an apologetic postscript. There is quite a long chapter on spinals, and the technique of lumbar puncture is described, but not a word is said about the desirability of wearing gloves, or even washing the hands before this procedure.

Though much effort has been made to instruct, the student who had only this book to guide him would fare badly.

Recent Advances in Oto-Laryngology. By F. BOYES KORKIS, M.B., Ch.B. (N.Z.), D.L.O. (Eng.), F.R.C.S., Surgeon and Dean, Metropolitan Ear, Nose and Throat Hospital; Senior Consultant Oto-laryngologist, Hillingdon Hospital. With a Foreword by R. SCOTT STEVENSON, M.D., F.R.C.S. (Ed.). Third edition. 8¼ × 5¼ in. Pp. 438+x, with 2 coloured plates and 144 text-figures. 1958. London: J. & A. Churchill Ltd. 60s.

THE third edition of this useful monograph is published under the editorship of Mr. Boyes Korkis, and he has taken over this task from Mr. Scott Stevenson, who writes a foreword.

Great progress has taken place in the branch of oto-laryngology in recent years and this monograph covers all the recent advances in this important subject.

The treatment of carcinoma of the larynx, so well presented in this book, should interest the general surgeon who is engaged in dealing with malignant disease.

Operative Surgery. Edited by CHARLES ROB, M.C., M.Chir., F.R.C.S., Professor of Surgery, St. Mary's Hospital, London; RODNEY SMITH, M.S., F.R.C.S., Surgeon, St. George's Hospital, London. Volume 6. Part X Hand, Pp. 105+x, Part XI Amputations, Pp. 71; Part XII Plastic Surgery, Pp. 131; Part XIII Gynaecology and Obstetrics, Pp. 123. Fully illustrated. 1958. London: Butterworth & Co. (Publishers) Ltd. £5 10s.

THE sixth volume of this comprehensive work on Operative Surgery deals with four large sections, namely, the hand, amputations, plastic surgery, and gynæcology and obstetrics. The treatment of congenital abnormalities of the hand are described and illustrated in an excellent way, with first-class drawings.

Sir Gordon Gordon-Taylor and Bernard Hand are in their element in describing the hindquarter amputation, an operative procedure which Sir Gordon has made his own.

One is delighted to see that Syme's amputation is described and well illustrated.

The section dealing with plastic surgery is admirable, and the drawings which illustrate it are excellent.

This volume is up to the same high standard as its five predecessors. An excellent production.

Ideals in Medicine. A Christian approach to medical problems. Edited by VINCENT EDMUNDS, M.D., M.R.C.P., and C. GORDON SCORER, M.B.E., M.D., F.R.C.S. 8¼ × 5¼ in. Pp. 192. 1958. London: The Tyndale Press. 12s. 6d.

THIS book can do nothing but good and should be read by every final-year medical student. There is a great scarcity of books on medical ethics and very little information is given on this subject in medical schools. It is a great pity that lectures are not included on medical ethics.

We are pleased to see that Dr. Vincent Edmunds and Mr. C. G. Scorer and their eleven other contributors have kept specially in mind the needs of final-year students

and younger qualified men and women. The subjects treated range from what is distinctive in the outlook of the Christian, through discussion of such matters as personal standards, the relationship of the family doctor to his patients and the satisfaction which he can derive from his work, to the ethical problems which arise in certain areas of medical practice, particularly in the realm of gynæcology, psychiatry, and clinical research.

There are two helpful appendices at the end of this book and an excellent bibliography.

Principles of Rectoscopy. By M. K. HERFORT and M. Z. MARATKA. 9½ × 6½ in. Pp. 254, with 78 illustrations, most of which are in colour. 1955. Prague: Státní. Zdravotnické Nakladatelstvi (1958, London: Constable and Co.). 42s.

THIS is a practical guide to the procedure of rectoscopy and sigmoidoscopy illustrated by a series of coloured drawings of the various conditions met with in the rectum and lower sigmoid.

The text is written in Czechoslovakian and an English translation is given.

The authors advocate the genupectoral position for sigmoidoscopic examinations as they think this gives a better overall picture of the interior of the lower colon.

There is nothing new in the text, but the coloured pictures are excellent. Should prove of value as an illustrated atlas of diseases of the rectum and sigmoid.

The Essence of Surgery. By C. STUART-WELCH, M.S., M.D., Ph.D., Professor of Surgery, Albany Medical College of Union University; and SAMUEL R. POWERS, Jun., A.B., M.D., M.Sc.D., Professor of Experimental Surgery, Albany Medical College of Union University. 9½ × 6 in. Pp. 320 + xiv, with 50 illustrations. 1958. Philadelphia and London: W. B. Saunders Co. 49s.

THIS is a unique book in many ways for it gives the modern surgeon not only the background of surgery but also select essays on essential subjects.

The phenomenon of bodily injury, the loss of body tissue, the loss of body fluids, infection, extirpative and reconstructive surgery, are but a few of the subjects discussed.

The historical side is well presented and this adds considerably to the usefulness of the book.

The authors approach their task in a critical manner and have some stimulating ideas on surgical investigation and research.

They state that: "A successful operation demands a detailed plan of attack, good asepsis, accurate hæmostasis and careful dissection. These principles are the keystones of operative surgery". And how right they are!

A stimulating book.

Connective Tissue. A Symposium organized by The Council for International Organizations of Medical Sciences. Edited by R. E. TUNBRIDGE, The University of Leeds. 9 × 5¾ in. Pp. 371 + xii, illustrated. 1957. Oxford: Blackwell Scientific Publications. 42s.

THIS volume contains the papers which were read in 1956 at a meeting in London arranged by the Council of International Organizations of Medical Sciences. The subject, connective tissue, is almost inexhaustible, but many and varied were the papers which were read dealing with different aspects of this peculiar tissue. Among the many aspects of the subject covered, a number of problems figured prominently: the nomenclature of the different preparations of collagen; the increasing importance of chemical analysis; the difficulty in obtaining pure extracts and the need to account for the small percentage of carbohydrate; the value of studying the growth of tissues as well as the mature fibres. Stress was laid on the existence of a family of collagens, and the possibility that elastin may yet prove to be an intimate member of the family.

The volume contains full reports of all the papers contributed together with the discussions which followed each paper.

An important book which will be used as a reference volume on connective tissues for many years to come.

The Year Book of General Surgery. Edited by MICHAEL E. DE BAKEY, B.S., M.D., M.S., Professor of Surgery and Chairman, Cova and Webb Mading Department of Surgery, Baylor University College of Medicine. With a section on Anesthesia edited by STUART CULLEN, M.D. 7½ × 5 in. Pp. 560, with 128 illustrations. 1957. Chicago: The Year Book Publishers Inc. (London: Interscience Publishers Ltd.) 57s.

AFTER some thirty-one years this book has a new editor because of the death of Evarts A. Graham in March, 1957. Mr. Warren H. Cole writes an excellent memorial to Dr. Graham which gives in detail the long list of his achievements and the many honours which were bestowed upon him. We had over the years become familiar with this excellent production and Dr. Graham certainly made the volume a most useful one.

We would like to congratulate Dr. Michael E. De Bakey on his first volume after taking over the editorship from Dr. Graham; he has succeeded well and the present volume is an excellent survey of what is important in surgery during the year 1957.

Although it is difficult to single out any particular section of this book for criticism, yet we would say that that part devoted to cancer of the breast is outstanding and gives the reader a very definite and conclusive reasoning as to the best method to treat this disease to-day.

An excellent production which every surgeon should read.

Injuries of the Bones of the Head. An Atlas of Clinical and X-ray Diagnosis. By J. VONDRA, M.D., Director of the Oral and Maxillofacial Surgery Department of the University Hospital of Prague, Vinohrady; and R. BLAHA, M.D., Director, X-ray Department, University Hospital, Prague, Vinohrady. 9½ × 6½ in. Pp. 304, with 170 illustrations. 1956. Prague: Artia (1958. London: Constable and Co.). 40s.

THIS is an excellent atlas of clinical and X-ray diagnosis written by two doctors from Prague. The radiographs are clear and instructive, while the coloured plates are superb.

The authors state that the purpose of this book is to serve as a guide to busy doctors in health centres and outpatients' departments, who are the first to be faced with the problem of resolving the signs and establishing the diagnosis, so important in the case of facial injuries.

In view of the fact that the incidence of injuries to the bones of the skull is showing a sharp increase with the development of motoring, it follows that prompt treatment is essential if good results are to be obtained.

This book should prove of value not only to practitioners but also to final-year students who wish to have a sound knowledge of injuries to the skull.

The Tissues of the Body. An Introduction to the Study of Anatomy. By W. E. LE GROS CLARK, F.R.S., Fellow of Hertford College, Dr. Lee's Professor of Anatomy in the University of Oxford. Fourth edition. 9¼ × 5¾ in. Pp. 415 + xii, with 127 illustrations. 1958. Oxford: Clarendon Press (Oxford University Press). 40s.

IT is just over twenty years since the first edition of this book appeared and from that date it has become one of the books which medical students have found useful. Now that histology is taught in anatomical departments and not in the physiological departments, it behoves the teaching anatomists to see that there is a suitable book on this subject. Professor le Gros Clark has written such a book and we confidently recommend it. Anatomy must be taught as a whole; the microscopic and macroscopic must be integrated.

There is a tendency to-day for medical students to rely on lectures and neglect reading; this is a great pity and this neglect should be remedied if possible. It is by the publication of such books as this, with its stimulating and intellectual outlook, that the medical student will be tempted to read more.

The illustrations throughout the book are excellent and well chosen.

The best introduction to the study of anatomy that has so far been published.

Reflexogenic Areas of the Cardiovascular System. By C. HEYMANS, M.D., Professor of Pharmacology, University of Ghent; and E. NEIL, M.D., D.Sc., John Astor Professor of Physiology, University of London, Middlesex Hospital Medical School. 9¾ × 7 in. Pp. 271 + viii, with 89 illustrations. 1958. London: J. & A. Churchill Ltd. 56s.

THIS book contains an excellent account of the physiology of the cardiovascular reflexes and the pharmacological effects exerted on these complicated mechanisms.

In these days, when so many new drugs are forthcoming, it is interesting to know how they act on the heart and its nervous connexions.

A complete discussion is presented on the work done in the last twenty-five years on the functional role of the baroceptor and chemoreceptor sino-aortic reflexes.

This book will not only be of value to the physiologist but also to the modern physician and cardiac surgeon who wishes to know more of the action of drugs on the peripheral receptors located in the aortic arch area. When arterial grafting is going ahead and portions of the aortic arch are replaced, the applied physiology and pharmacology of the area is important.

There are twenty-seven pages of references and every paper covering this subject is included, which makes this book an important reference volume.

Sherrington: Physiologist, Philosopher and Poet. By LORD COHEN OF BIRKENHEAD, M.D., D.Sc., LL.D., F.R.C.P., F.A.C.P., F.F.R., F.S.A., J.P., Professor of Medicine, University of Liverpool. 8½ × 5½ in. Pp. 108 + xiv, with 17 illustrations. 1958. Liverpool: Liverpool University Press. 17s. 6d.

"THE Sherrington Lectureship at the University of Liverpool was founded in 1948 in honour of Sir Charles Scott Sherrington, O.M., G.B.E., M.D., F.R.S. (1857–1952) in recognition of his outstanding contributions to Physiology and Medicine in general, and, in particular, of his association with the University as George Holt Professor of Physiology from 1895–1913.

"The duty of the lecturer shall be to deliver a lecture or course of lectures making a contribution to any subject related to the Faculties of Medicine and Science. The appointment of the lecturer shall be made biennially."

This book contains the three lectures given by Lord Cohen, who was the fourth lecturer appointed. In order to form a composite picture of his subject he decided to give a course of three lectures, the first being devoted to Sherrington the Man, the second to the Physiologist, and the third to the Philosopher and Poet, thereby earning the gratitude of the "informed non-specialist". In the preface the author rightly makes no apology for a physician delivering this course of lectures, for we are mindful that in 1946 at the age of 89 years Sherrington published a book, *The Endeavour of Jules Fernel*, who, like the lecturer, was "already a physician greatly occupied in practice and teaching".

Jules Fernel, philosopher and physician, published in Paris in 1542 a book entitled *The Natural Part of Medicine* which Sherrington regarded as the first treatise on physiology since that entitled *The Use of the Parts* written by Galen fourteen centuries before. Fernel's book met a need and was re-issued many times; later he changed the title to *Physiology* (1554). This was the first use of this name, which has remained ever since. It remained the treatise on the subject until it was supplanted by William Harvey's *De Motu Cordis* (1628), which is the foundation of modern physiology. Sherrington's book, *The Integrative Action of the Nervous System*, published in 1906 and based on the lectures given by him under the Silliman Foundation at Yale University in 1904, has been described, nearly fifty years later, by Professor John Fulton, a previous Sherrington Lecturer, as ranking "in importance with Harvey's *De Motu Cordis*, for it marked a turning point in the history of physiological thought".

Charles Sherrington was born in 1857, the son of a doctor practising in Norwich, and although his father died during Charles's childhood, he was fortunate in having for his stepfather one who was "a medical man, a fine scholar, a notable archæologist, a geologist, and a lover of the arts, from whom he learned an appreciation of the classics, of poetry, of Gothic architecture and painting". These tastes remained with him during his whole life. The outstanding contributions Sherrington made to the elucidation of the physiology of the nervous system is acknowledged by the specialist. The three lectures which constitute this book will undoubtedly fulfil the aim of Lord Cohen, whose object was "to describe and assess with the aid of diagrams and films his contributions to learning . . . for the informed non-specialist . . . so that he may marvel at a productivity—monumental, magnificent and sustained—covering a span of seventy years and which embraced not only science, but also philosophy, history and poetry".

Sherrington's interest in physiology began during his undergraduate days while a student at Caius College working for the Natural Science Tripos in the School of Physiology at Cambridge, where Sir Michael Foster was the professor, with Gaskell, Langley, and Lea as members of the department. He obtained a First in 1882 in Part I and a First with Distinction 1883 in Part II. During 1883 he was Student Demonstrator in Anatomy to Professor Sir George Humphry. He continued his clinical studies at St. Thomas's in 1884, and qualified in 1885.

Sherrington published his first paper in conjunction with Langley in 1884 while still a student, "the first paper of over 320 which were to bear the name of Sherrington". A list of these with their titles and tabulated according to the year of publication are given at the end of the book. In 1884 he had gained the George Henry Lewes Studentship for Physiological Research and spent nearly a year working in the physiological laboratory at Strasburg under Professor Goltz, thereby increasing his training in experimental physiology. "In 1885, at the age of 28, he was deputed by the Association for Research in Medicine, in conjunction with the Royal Society and University of Cambridge, to accompany C. S. Roy, later

the first Professor of Pathology in Cambridge, and J. J. Graham Brown, an Edinburgh physician, on a mission to Spain to investigate an outbreak of Asiatic cholera. Sherrington was the best linguist of the three and conducted the negotiations." They found the causative bacteria and recorded their findings in the *Proceedings of the Royal Society* (1886). This journey, in addition to other things, kindled Sherrington's interest in Spanish art, literature and drama, and "began his lifelong friendship with Ramón y Cajal who was to elucidate the structure of the nervous system with the same penetrating brilliance that Sherrington was to shed upon its function". He then proceeded to work with Rudolf Virchow and Robert Koch in Berlin. In 1887 he was elected a Fellow of his College and Lecturer in Systematic Physiology at St. Thomas's Hospital.

The Brown Institution of the University of London had been founded in 1871 "for research into diseases of animals useful to man". Sherrington was appointed in 1891 to be Physician Superintendent in succession to Sir Victor Horsley, which gave him increased opportunities for research projects and also enabled him to meet leaders of the medical and veterinary professions. During this period he published many classical papers on the spinal cord, nerve-roots, and reflex action. In 1893 he was elected F.R.S. at the age of 36. During the next few years Sherrington initiated his researches on motor and sensory segmentation. His work on reflex action forms the solid foundation of how the central nervous system performs its functions. This is all detailed and explained with beautifully clear line diagrams in the second lecture. In 1895, when his reputation as a research physiologist was accepted by all, he was appointed Professor of Physiology at the University of Liverpool, and remained as such until 1913, when he accepted the invitation to occupy the Wayneflete Chair as Professor of Physiology at Oxford, which he occupied until 1935. It was while he was at Liverpool that he carried on the researches which led to the book *The Integrative Action of the Nervous System*. He continued his work on the localization of function in the brain and on the reflexes. These latter afforded an explanation on the rigidity resulting from hemiplegia, etc. His work and researches were also instrumental in explaining the physiological basis of the clinical signs in disease of the central nervous system. This work led him logically to study the philosophical relationship between the mind and the brain. In the third lecture Lord Cohen examines Sherrington's ideas which formed the basis of the Rede Lecture in 1933 and the Gifford Lectures delivered in 1937–8, subsequently published in 1940 under the title *Man on his Nature*. The third lecture contains many quotations from these sources but, at the present time, with no definite conclusion. With the interests formed in his childhood and early years it was natural that Sherrington, in his periods of relaxation, should turn to the reading and writing of poetry. "Sherrington's scientific and philosophical writings are strewn with apt quotations which reveal an enviable intimacy with the poets." When, for example, he refers to the suggestion that sleep is induced by blocking the pathway of sensory impulses to the roof brain, he recalls the lines—

> "Turn the key deftly in the oiléd wards,
> And seal the hushéd casket of my soul."

And he observes: "It is as though Keats 130 years ago had fore-known the mechanism involved." Sherrington wrote many poems during the war years (1914–18) and in 1925 published *The Assaying of Brabantius and other Verses*. This was dedicated to Sir Henry Head, Physician at the London Hospital, who was himself the author of *Destroyers and other Verses* (1919). Lord Cohen includes some quotations from it in the third lecture.

If poetry is life touched with emotion then it would seem that a physician is peculiarly fitted to write it and many have done so. Only one medical man, the late Dr. Robert Bridges, has been holder of the office of 'Versificator Regis' among the nineteen who have been thus honoured since Edmund Spenser was the first appointed in 1519, but many have been worthy.

Poetry has been and is used as a therapeutic agent with success by many in times of emotional stress and anxiety. This is understandable if poetry is articulate music, as Dryden maintained. Medicine affords many examples of poetry, or at any rate rhyming, being used as a means of communicating knowledge. To give only a few examples, there is the *Regimen Sanitatis of Salerno* (A.D. 1100), *Syphilis sive Morbus Gallicus* (written in 1521 and published 1530), by Girolamo Frascastoro of Verona, *The Famous Art of Preserving Health* (1744), by John Armstrong, and many others. Volumes have been written on the allusions to medicine in Shakespeare's plays. Few have been equally distinguished as medical men and as poets; perhaps Oliver Wendell Holmes came nearest to that ideal and Weir Mitchell ran him very close. It is related that the latter, as a budding poet, wrote to 'The Autocrat of the Breakfast Table' for advice in his literary aspirations. The advice was to confine his efforts *in* his desk until well established in medicine and about the age of 40. On the grounds of heredity there is relationship between poetry and physic for Apollo, the god of poetry and culture, was the father of Aesculapius, the titular divinity of the healing art, and in days gone by those who practised medicine were dignified as 'the children of Apollo'.

These lectures should be read and pondered by all interested in medicine, its basis, history, and development. After having read them, scanned the list and wide canvas of the papers published by Sherrington, and then the details given at the end of the book taken from the last published edition of *Who's Who* before his death in 1952, one marvels how he could have found time, which he did, to help other men. The mass of work which he produced out of his own laboratory leaves the impression that he could have had no part in any life beyond its walls.

The three plates depicting the likeness of Sherrington which are included in the book as a frontispiece to each lecture, particularly the portrait by Augustus John, reflect the penetrating intellect, imagination, shrewdness, wide culture, and genius of the man, mingled with kindness, courtesy, and tolerance.

The lecturer has undoubtedly fulfilled the requirements demanded of him "to make a contribution to a subject related to the Faculties of Medicine and Science".

Microscopic Anatomy of the Temporal Bone. By DOROTHY WOLFF, A.B., M.A., Ph.D., Research Pathologist, Manhattan Eye, Ear and Throat Hospital; RICHARD J. BELLUCCI, B.S., M.S., M.D., Surgeon-in-Charge, Speech and Hearing Clinic, Manhattan Eye, Ear and Throat Hospital; and ANDREW A. EGGSTON, B.S., M.D., Pathologist and Director of Laboratories, Manhattan Eye, Ear and Throat Hospital. 9½ × 7½ in. Pp. 414 + x, with 199 illustrations. 1957. Baltimore: Williams and Wilkins Co. (London: Baillière, Tindall & Cox). 100s.

THIS large monograph is in reality a photographic survey of serial sections of the temporal bone cut in the three routine planes of sectioning human specimens. It is a great addition to our knowledge of the complicated internal anatomy of the temporal bone. The only collection of similar sections of the temporal bone was given by the late Mr. Arthur Cheatle to the Royal College of Surgeons of England, and it was completely destroyed by enemy action during the First World War.

In the past the surgery of the temporal bone was mainly devoted to the eradication of infection, but this

infection to-day is largely controlled by antibiotics. However, the fenestration operation with its modern surgical approach has shed a new light on the internal anatomy of the temporal bone, and it behoves all surgeons who are dealing with the surgery of the ear to have an extensive knowledge of the minute, almost microscopic, anatomy of the temporal bone.

Although this monograph was compiled primarily for specialists in otology, yet the anatomist and pathologist will find it an excellent reference volume. Also the neurosurgeon will find much which will interest him within the pages of this book.

The 199 figures which illustrate this volume are beautifully reproduced. These figures are divided into three series: those cut in the horizontal plane, those cut at right angles to the long axis of the petrosa, and those cut in the plane of the long axis of the petrosa.

An excellent production.

Ulcerative Colitis. By HARRY E. BACON, B.S., M.D., Sc.D., LI.D., F.A.C.S., F.A.P.S., Professor and Head of Department of Proctology, Temple University Medical Center, Philadelphia, Pa. With a Foreword by ALTON OCHSNER, B.A., M.D., Sc.D., F.A.C.S., F.A.P.S., Professor of Surgery, Tulane University School of Medicine; Director of Surgery, Ochsner Clinic and Ochsner Foundation Hospital, New Orleans. 10 × 6¾ in. Pp. 395 + xx, with 183 illustrations. 1958. Philadelphia: J. B. Lippincott Co. (London: Pitman Medical Publishing Co. Ltd.). 120s.

THIS is a comprehensive monograph which covers the subject of ulcerative colitis in a very interesting and practical manner. The volume is dedicated to Alton Ochsner, who writes a foreword and states that: "There are few conditions that have presented greater problems in therapy and more controversy than chronic ulcerative colitis." We agree with this statement, but surely we are better equipped to deal with this problem to-day than we were a decade ago.

The author deals with the condition from every angle, and, after considering the many and various theories brought forward to explain its aetiology, he puts forward a detailed description of the pathological processes which make up this disease.

The surgical approach to this disease is well presented and illustrated with some excellent drawings. The actual operative technique of ileostomy is well described.

Any clinician who has to treat cases of ulcerative colitis, be he physician or surgeon, will require to have this book for constant reference.

Cardiovascular Collapse in the Operating Theatre. By HERBERT E. NATOG, M.D., Assistant in Anesthesia, University of Illinois, College of Medicine; and MAX S. SADOVE, M.D., Professor of Surgery (Anesthesiology), University of Illinois College of Medicine. With a Foreword by WARREN H. COLE, M.D. Pp. 197 + xvi. 1958. London: Pitman Medical Publishing Co. Ltd. 45s.

THE time is ripe for the publication of such a book as this. During the last decade much literature has accumulated on the important subject of cardiovascular collapse in the operating theatre.

This monograph gives an excellent and very practical review of the many phases of cardiovascular collapse or cardiac arrest in the operating room. All the many predisposing and precipitating factors are considered in detail.

A very complete discussion on the causative factors is presented and this includes a comprehensive consideration of pre-existing disease, errors in anæsthesia, inadequate pre-operative preparation, excessive operative load on a weakened myocardium, and electrolyte disturbances.

This book will prove of real value not only to anæsthetists, but also to all surgeons who undertake major surgical procedures.

Clinical Neuro-surgery. The Proceedings of the Congress of Neurological Surgeons, Chicago, Illinois, 1956. Volume 4. 9 × 5¾ in. Pp. 142 + x, fully illustrated. 1957. Baltimore: Williams & Wilkins Co. (London: Baillière, Tindall & Cox). 56s.

THE fourth volume of *Clinical Neurosurgery* records the edited proceedings of the Congress of Neurological Surgeons held in Chicago in November, 1956. It is dedicated to Dr. Wilder Penfield, whose introductory paper is on Hippocrates, and except for this and his article on the temporal cortex, contains a series of papers on pituitary and parapituitary lesions and their treatment and on the physiological effects of pituitary extirpation. Hypophysectomy for cancer of the breast is discussed in an article by Bronson S. Ray, which is followed by one on the physiological effects of hypophysectomy by Olaf H. Pearson. After hypophysectomy the adrenals fail to produce hydrocortisone and the production of the androgenic and œstrogenic steroids is suppressed, but aldosterone production is not impaired. It is interesting to notice how the development in our knowledge of pituitary function has arisen from the surgical attacks which have recently been made on the gland, and we now know that diabetes insipidus may develop even when the anterior lobe substance has been completely extirpated. Experimental work on animals had led us to believe that the anterior lobe was necessary for the development of the condition, but it appears to be the result of degeneration of the supra-optic and paraventricular nuclei. C. W. Rucker, J. D. Camp, J. G. Love, and the late Gilbert Horrax also contribute chapters to this well-produced volume, which will have a strong appeal to all who are interested in the central nervous system and particularly to those concerned with the surgical aspects of neurology.

Transactions of the International Society of Plastic Surgeons. First Congress, Stockholm and Uppsala, 1955. Edited by TORD SKOOG, M.D., General Secretary of the Congress, in co-operation with ROBERT H. IVY, M.D., and the Editorial Board of Plastic and Reconstructive Surgery. 10 × 6¾ in. Pp. 568 + xvi, with 467 illustrations. 1957. Baltimore: Williams & Wilkins Co. (London: Baillière, Tindall & Cox). 160s.

THIS large volume contains the reports and lectures delivered by numerous plastic surgeons who attended the First International Congress in Stockholm in 1955. More than 300 plastic surgeons attended from forty-one countries.

Plastic surgery to-day is a large branch of surgery and covers a vast field, as can be seen by reading this book.

The problem of the treatment of burns has become the province of the plastic surgeon and is an important one in peace as well as war time. This volume contains very many articles from surgeons from different parts of the world and the varied methods of skin-grafting are well presented and illustrated.

The chapters include the various methods of plastic surgery used in dealing with conditions of the eye, ear, scalp and cranium, œsophagus, breast, abdomen, genitals, and hand. There are also chapters devoted to clinical and experimental research.

The volume contains a wealth of material with many excellent illustrations, and no plastic surgeon can afford to be without this book.

The Cerebrospinal Fluid. A Ciba Foundation Symposium. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch.; and CECILIA M. O'CONNOR, B.Sc. 8 × 5 in. Pp. 335 + xii. Fully illustrated. 1958. London: J. & A. Churchill Ltd. 50s.

THIS is a record of the contributions made at a Ciba Foundation Symposium which was suggested by the late G. B. Wislocki, whom it was hoped would play an important part in it, but who died before it was held in May, 1957. The chairman was Professor G. A. G. Mitchell, of Manchester, whose opening remarks introduce the various papers, which deal with the development and functions of the choroid plexuses, the nature of the fluid, its source and movements, and the innervation of the meninges and choroid plexuses. There is apparently an intimate association of nerve-fibres with blood-vessels, but an absence of definite nerve-endings in either the meninges or the choroid plexuses. An interesting relationship of the pressure and quantity of the cerebrospinal fluid to either a deficiency or abundance of vitamin A is recorded. Due reference is made to the pioneering work of L. H. Weed, whose contributions to our knowledge of the anatomy and pathology of the cerebrospinal fluid have mostly stood the test of time. The consensus of opinion still favours the view that, with a possible exception during early fœtal life, the chief function of the choroid plexuses is the production of the cerebrospinal fluid. Some references follow each of the fifteen papers comprising the volume, which is well printed and illustrated, and after each paper the remarks made by the various speakers are recorded in smaller type.

Those interested in the nervous system will find here an up to date account of what is known of the production, circulation, and absorption of the cerebrospinal fluid and some of the problems which still appertain to it.

Cancer. Edited by RONALD W. RAVEN, O.B.E. (Mil.), T.D., F.R.C.S., Joint Lecturer in Surgery, Westminster Medical School, University of London; Volume 1. Pp. 539 + x, with 94 illustrations. Volume 2. Pp. 641 + x, with 357 illustrations. 1958. London: Butterworth & Co. (Publishers) Ltd. 85s. per volume.

VOLUME 1 of this great work is devoted to a consideration of the causation of cancer, and contains some outstanding essays. Amongst many worthy contributions some are of quite exceptional value. Professor J. N. Davidson discusses the chemical mechanisms of cell division. This entails a description of the structure of R.N.A. and D.N.A. together with the part which these substances play in mitosis. Dr. Leon Dmochowski discusses the significance of viruses in the origin of avian, rodent, and murine tumours, and the Bittner agent is fully described. The author of this section analyses the electron microscopic findings in human milk and points out how there is by no means a necessary correspondence between the appearance of particles in the electron microscope alleged to be the Bittner virus and a positive result from biological tests for this virus. The nature of these particles must therefore remain in doubt. An excellent contribution on the genetic component of cancer by Professor Koller carries on the story of R.N.A. and D.N.A. This author describes the abnormal mitoses characteristic of the cancer cell, emphasizing the 'stickiness' which modifies the chromosomal behaviour, particularly in the telophase. Chromosome numbers are analysed and the target theory of mutation and cancer is propounded. Finally, the genetics of 'cancer families' is dealt with, and Cuthbert Dukes' work on congenital polyposis of the colon receives worthy treatment.

A final chapter on the carcinogenic effects of radiation by A. Glucksmann, L. J. Lamerton, and W. T. Mayneord deals with radiation-induced cancer in man, citing examples from the New Jersey luminous dial painters and the Hiroshima and Nagasaki victims. Iatrogenic cancer following radiation therapy for thymic tumours, spondylitis, and innocent bone lesions is discussed and suitable warnings are given.

In addition to the articles specially selected for mention many other matters of great importance are discussed, including the effects on cancer of hormones, nutrition, and environment. Sir Ernest Kennaway has written on cholesterol, Dr. Peacock contributes a most informative section on carcinogenesis, and Dr. Griffin writes on the biochemistry of cancer induction.

In Volume 2 there are a number of short articles describing the macroscopic and microscopic anatomy of cancer in different regions. If Volume 1 is a volume for study, Volume 2 is essentially a volume for reference. Following an excellent introductory chapter by Professor Cunningham on the pathology of tumours in general, and chapters on the biological characteristics of neoplasia and their modes of spread, the latter by Professor R. A. Willis, there are twenty-nine articles by various authors on cancers of different organs and a final article on cancer in children.

The editor deals with cancer of the pharynx and œsophagus and the authors chosen to write about other organs—Cuthbert Dukes on the rectum, Rodney Smith on the pancreas, Edith Dawson on the breast, A. C. Thackray on the salivary glands, and so on—attests the authority which this work must command.

There can be very few faults to find with this symposium which is a monument to British cancer research, albeit a few of the contributions hail from as far away as Texas, Hong Kong, and Sydney. In the chapter on connective-tissue tumours it is curious to find no reference to Stanford Cade's classic paper on muscle sarcoma, and some of the references in other chapters allude to papers rendered obsolete by subsequent work—a defect no doubt inevitable when the time taken to collect contributions from so many authors scattered all over the world is considered.

Mr. Ronald Raven is to be congratulated on a great contribution to scientific advance.

Intestinal Obstruction. By CLAUDE E. WELCH, M.D., D.Sci.(Hon.), Visiting Surgeon, Massachusetts General Hospital; Clinical Associate in Surgery, Harvard Medical School. $8\frac{5}{16} \times 5\frac{3}{4}$ in. Pp. 376, with 135 illustrations. 1958. Chicago: The Year Book Publishers Inc. 79s.

INTESTINAL obstruction is an all-embracing subject, for the whole medical profession is interested in it. The student, the practitioner, the clinician, and the surgeon all have a keen concern in this all too common condition.

Mr. Welch has drawn upon his ripe and extensive clinical experience in writing this book. He has covered this extensive subject in a very practical and interesting manner and his advice on difficult cases is very sound.

To-day more than ever before the radiologist has come to the aid of the surgeon, and more cases of correct pre-operative diagnoses are forthcoming. The pre-operative treatment in the shape of gastric and intestinal suction, the correction of the fluid balance, and the various relaxant drugs have proved of great value to the abdominal surgeon.

The various antibiotics which can be used after operation and their influence in preventing peritonitis have played their part in the successful treatment of intestinal obstruction.

All these many factors are well portrayed in this monograph.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.]

Clinical Reports of the Adelaide Children's Hospital. Volume 3, Number 1. 1956–7. 9¾ × 7 in. Fully illustrated.

Year Book of Urology (1957–8 Series). Edited by WILLIAM WALLACE SCOTT, M.D., Ph.D., Director, James Buchanan Brady Urological Institute, The Johns Hopkins Hospital; Urologist-in-Charge, The Johns Hopkins Hospital; Professor of Urology, The Johns Hopkins University School of Medicine. 7⅝ × 5 in. Pp. 359, with 79 illustrations. 1958. Chicago: The Year Book Publishers Inc. 57s.

Cancer. Edited by RONALD W. RAVEN, O.B.E. (Mil.), T.D., F.R.C.S., Joint Lecturer in Surgery, Westminster Medical School, University of London; Surgeon, Westminster Hospital Teaching Group; Surgeon, The Royal Marsden Hospital. Vol. 3. 9½ × 6¼ in. Pp. 483 + x, fully indexed, with 165 illustrations. 1958. London: Butterworth & Co. (Publishers) Ltd. 85s.

Young Children in Hospital. By JAMES ROBERTSON, with a Foreword by RONALD MACKEITH, D.M., F.R.C.P. 7⅝ × 4¼ in. Pp. 103 + iv. 1958. London: Tavistock Publications Ltd. 4s. 6d., paper covered.

Fifty Years of Neurosurgery. By ERNEST SACHS, M.D. 7 15/16 × 5 in. Pp. 186, with 15 illustrations. 1958. New York: Vantage Press. $3.50.

Orr's Operations of General Surgery. By GEORGE A. HIGGINS, M.D., F.A.C.S., Associate Professor of Surgery, University of Kansas School of Medicine; and THOMAS G. ORR, jun., M.D., F.A.C.S., Associate in Surgery, University of Kansas School of Medicine. Third edition. 10 × 7 in. Pp. 1016 + vi, with 835 illustrations. 1958. Philadelphia and London: W. B. Saunders Co. 140s.

Orthopedic Diseases. By ERNEST AEGERTER, M.D., and JOHN A. KIRKPATRICK, jun., M.D. 9¾ × 6¼ in. Pp. 602 + xii, with 354 illustrations. 1958. Philadelphia and London: W. B. Saunders Co. 87s. 6d.

L'Auto-intoxication après Brûlure. By T. GODFRAIND. 9½ × 6½ in. Pp. 191, with 49 illustrations. 1958. Bruxelles: Editions Arscia. 250 fr. belg.

Diseases of the Colon and Rectum. Vol. I, No. 2, March-April, 1958. 10 × 7 in. Pp. 79 + xvi, fully illustrated. Philadelphia: J. B. Lippincott Co. (London: Pitman Medical Publishing Co. Ltd.). 6 volumes per annum, 100s.

Medizin: Theorie und Klinik in Einzeldarstellungen. Vol. II. Die Angeborene Huftgelenksverrenkung und Ihre Behandlung. By GUSTAV HAUBERG, Head of Orthopædic University Clinic, Frankfurt. 9 × 5¾ in. Pp. 142, with 58 illustrations. 1958. Heidelberg. D.M. 19.80.

Traumatologie Infantile. By P. L. CHIGOT, P. ESTÈVE. 10⅜ × 6 in. Pp. 357, with 114 illustrations. 1958. Paris: Expansion Scientific Française. 5000 fr.

A Text-book of X-ray Diagnosis. By British Authors, in four volumes. Edited by S. COCHRANE SHANKS, C.B.E., M.D., F.R.C.P., F.F.R., Director, X-ray Department, University College Hospital, London; and PETER KERLEY, C.V.O., C.B.E., M.D., F.R.C.P., F.F.R., D.M.R.E., Director, X-ray Department, Westminster Hospital, London. Third edition. Vol. III. 9¾ × 7 in. Pp. 883 + xvi, with 802 illustrations. 1958. London: H. K. Lewis & Co. Ltd. 120s.

Tracheotomy: a Clinical and Experimental Study. By THOMAS G. NELSON, Major, M.C., U.S.A.R. 10 × 6½ in. Pp. 111 + vi, with 47 illustrations. 1958. Baltimore: The Williams & Wilkins Co. (London: Baillière, Tindall & Cox). 30s.

Medicine and the Navy, 1200–1900. By J. J. KEEVIL. Vol. II, 1649–1714. 8¾ × 6¾ in. Pp. 332 + xii, with 18 plates. 1958. Edinburgh and London: E. & S. Livingstone Ltd. 40s.

Operative Surgery. Edited by CHARLES ROB, M.C., M.Chir., F.R.C.S., Professor of Surgery, St. Mary's Hospital, London; and RODNEY SMITH, M.S., F.R.C.S., Surgeon, St. George's Hospital, London. Vol. 8. 11 × 8¾ in. Part xvi: Neurosurgery, pp. 5–57 + xv; Part xvii: Eyes, pp. 5–83; Part xviii: Ear, Nose and Throat, pp. 5–196. Fully illustrated and indexed. 1958. London: Butterworth & Co. (Publishers) Ltd. 110s.

The Nuffield Provincial Hospital Trust. Fourth Report. 8½ × 5½ in. Pp. 70. 1958. Oxford: Oxford University Press.

Abdominal Operations by the Vaginal Route. By PAUL WERNER, M.D., Late Professor of Gynæcology and Obstetrics, University of Vienna; and JULIUS SEDERL, M.D., Vienna. Translated by L. M. SZAMEK, M.D. 10 × 6¾ in. Pp. 165 + x, with 120 plates. 1958. London: Pitman Medical Publishing Co. Ltd. 65s.

Pediatric Surgery. By ORVAR SWENSON, Surgeon-in-Chief, The Boston Floating Hospital for Infants and Children; Professor of Pediatric Surgery, Tufts University School of Medicine. 9¾ × 6¾ in. Pp. 740 + xvi, with 980 illustrations. 1958. New York: Appleton-Century-Crofts, Inc. $20.00.

Modern Trends in Anæsthesia. Edited by FRANKIS T. EVANS, M.B., B.S., F.F.A.R.C.S., D.A.; and T. CECIL GRAY, M.D., F.F.A.R.C.S. 9½ × 6½ in. Pp. 318 + x, with 29 illustrations, fully indexed. 1958. London: Butterworth & Co. (Publishers) Ltd. 67s. 6d.

Fractures and Dislocations. By GEORGE PERKINS, M.C., M.Ch., F.R.C.S., Consulting Orthopædic Surgeon, St. Thomas's Hospital, London. 9½ × 6 in. Pp. 363 + viii, with 255 illustrations. 1958. London: University of London—The Athlone Press. 57s. 6d.

The Postoperative Chest. Radiographic Considerations after Thoracic Surgery. By HIRAM T. LANGSTON, M.D., ANTON M. PANTONE, M.D., and MYRON MELAMED, M.D. 10 × 6¾ in. Pp. 228 + xviii, with 80 illustrations. 1958. Springfield, Ill.: Charles C. Thomas (London: Blackwell Scientific Publications). 60s.